THE EVOLUTION OF MODERN OBSTETRICS *

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IN Glasgow forty years ago, when I was a medical student, childbirth was a dangerous and wasteful process. Out of 19,000 women admitted to the Glasgow Maternity Hospital between 1925 and 1929, 542 died. Eclampsia occurred in 395 cases, with a maternal case-mortality of 18%. There were 226 deliveries following craniotomy, and 11% of the mothers died. Few medical students were aware of all this death and destruction, since they were seldom in the wards or labour rooms and never attended antenatal clinics. Clinical obstetrics consisted of (1) sitting in a large amphitheatre and watching our teachers perform cæsarean sections and various types of vaginal operation, and (2) conducting domiciliary deliveries with a fellow student. Since we were unsupervised and had received no practical instruction before setting out " on district ", we were quite unable to render any effective treatment, nor were we allowed to give drugs to relieve pain or check bleeding. I can still recall vividly our feeling of inadequacy, although fortunately the patients seemed surprisingly grateful for the little we did for them.

That such experiences were not peculiar to Glasgow is shown by the following excerpt from a letter from Sir Eardley Holland:

" The change since my student days is unbelievable! As I had stayed on in the Anatomy and Physiology Departments to take my primary F.R.C.S. exam. I arrived at the Hospital too late (or too early) to begin my surgical and medical dressing and clerking, so the Dean said ' Do your Midder and get it out of the way ', which I did. It was one month (with another student) on the Extern. district. There was no in-patient midwifery teaching; any obstetric emergencies were taken into the Gyn. ward.

" The Resident House Accoucheur showed me how to make a P.V., and gave me a few tips, and, armed with these *plus* a ' little red Herman ' in my pocket, I went to live in a bedroom (with my fellow student). We had meals at the Hospital and also deloused ourselves, naked on a sheet, on the floor every night. The Hospital then was on one side of a big slum (now long demolished).

" The first case I had was about midnight. The husband took me to a room in a slum house where he and his family lived and slept and he worked at boot-repairing. I duly made a P.V.; when my finger was withdrawn it was covered with a lot of horrid looking black stuff.

" Thinking something mysteriously dreadful must have happened in the poor woman's inside, I hastened back to the Hospital to fetch the Resident Accoucheur. I had gone only a couple of hundred yards when I heard running feet behind me. It was the breathless husband who panted—' For Gawd's sake, Doc, come back, the baby's bein' born! ' Back we tore and I found the body of the babe outside but the head still in. This must be what my ' little Red Herman ' calls a breech presentation, said I. I wrenched out the head as best I could, but alas, the babe was dead.

" That was the year 1901. A good bit of evolution since then, I guess! "

In the Glasgow Maternity Hospital, during the 1920s, we were dealing with a concentration of abnormal midwifery, the like of which has probably never been seen anywhere else in Britain; but the state of midwifery all over the country was bad, and national inquiries showed both in England and Wales and in Scotland that many deaths could have been avoided.

In 1935, it became possible to take effective measures against sepsis, the greatest cause of maternal mortality at that time. Other advances followed, and in many areas the maternal death-rate has now almost reached an irreducible minimum. It might be thought that standards of obstetric care are now about optimal. Yet the study of fœtal mortality indicates that we have no cause to be complacent; for example, in England and Wales, the stillbirth-rate is higher than in many other countries, and has been almost stationary for over a decade.

Maternal Mortality

In the Glasgow Royal Maternity Hospital in the 1920s, there was an average of 2 maternal deaths every week, and we were so preoccupied with the problem of keeping the mother alive that the very high fœtal mortality was very seldom discussed.

The City of Glasgow helped to pioneer the industrial expansion of the 19th century and became one of the places " where wealth accumulates and men decay ". Many of its inhabitants lived in degradation, crowded together in tenement slums. Few of the slum children, after weaning, ever drank milk except in the smallest quantities, and smoke from factories and domestic coal fires shut out the sun. Rickets was so common that Glasgow surgeons became famous for their skill in performing osteotomy to straighten crooked legs, and obstetricians for their skill in the complicated vaginal operations made necessary by deformed pelvic bones. To the extent that the long struggle against deficiency disease is virtually over, our population may now be considered well nourished, but minor degrees of malnutrition no doubt still exist and many of the mothers of today are stunted by the malnutrition they experienced as children during the 1930s.

Rural areas escaped many of the ill effects of industrialisation, and country women were therefore taller, better developed physically, and generally healthier than those in the cities. Despite this, examination of the maternal mortality statistics of thirty years ago shows that there was little difference in the overall rates of city and country districts. In the rural areas the death-rate from puerperal sepsis was generally lower because the greater isolation of cases hindered the spread of the hæmolytic streptococcus. Difficult labour due to disproportion was almost certainly less in rural areas. But lack of specialist help, inadequate communications, and deficiencies in transport increased the mortality from such sudden and serious conditions as eclampsia and antepartum and postpartum hæmorrhage. The advantages and disadvantages of rural life thus almost exactly cancelled each other out, giving an overall maternal mortality-rate not very different from that of the cities.

The two main reasons for the excessive maternal mortality in the past were (1) ignorance of the causes of many of the serious complications of pregnancy and labour and the inadequacy of the methods of treatment

* The Ingleby lectures delivered in Birmingham on May 18, 1960.

available, and (2) the lack of a well-organised maternity service staffed by well-trained doctors and midwives. Until as recently as 1937, when the Maternity Services (Scotland) Act was passed, it was legal in Scotland for an untrained woman to attend a mother in labour for gain.

Sepsis

By far the most important cause of maternal deaths, both in the cities and in country districts, was puerperal sepsis. Even after a labour that had been entirely normal, a rigor on the second or third day, accompanied by a sudden rise of temperature and pulse, could mean death within a week from septicæmia or peritonitis. The clinical features were well known to the women themselves and to the handywomen in attendance. The profession was very reluctant to admit that the doctor or midwife was often the carrier of the streptococcus and indeed sometimes the primary source of the infection; yet in 1795, Alexander Gordon of Aberdeen, after a simple epidemiological investigation, had been able to say: "... this disease seized such women only as were visited or delivered by a practitioner or taken care of by a nurse who had previously attended patients affected with the disease. In short, I had evident proofs of its infectious nature." (Quoted by Porter 1958.)

Before 1935, research on methods of typing streptococci had made it possible to chart without doubt the source and mode of spread of the organism responsible for most cases of puerperal sepsis. This led to the identification, control, and treatment of carriers among nurses, doctors, students, and others, the use of masks, and the immediate isolation of infected cases. Although these measures led to some decrease in the incidence of streptococcal sepsis, it was difficult to get them carried out really effectively. Fortunately the sulphonamides were introduced in Britain very soon afterwards.

Penicillin, which is now used instead of the sulphonamides, is still remarkably effective against the streptococcus. The rise in the incidence of drug-resistant organisms in most maternity hospitals in recent years has not, so far, increased the maternal death-rate from sepsis; but it has underlined the need to practise the principles of isolation and barrier nursing if maternity hospitals are to be kept safe for the mother and more especially the child. In the overcrowded and understaffed hospitals of today we have come to rely too much on chemotherapy. The need to design hospitals so that the risk of sepsis is reduced to a minimum is as important as ever it was. It would be most unfortunate if outbreaks of sepsis should curb the work of our maternity hospitals at a time when they are capable of doing so much for the safety and comfort of the mother and baby.

Hæmorrhage

The death-rate from hæmorrhage in Scotland did not begin to fall till after 1941, when blood-transfusion services based on blood-banks came into being, largely under the stimulus of war. The rate of fall was most rapid after 1947, presumably because the ending of the war released for civilian duties large numbers of young doctors experienced in the treatment of acute hæmorrhage and shock.

It is hard to realise how little blood was given twenty-five years ago, even in our large maternity hospitals. Since blood-banks had not been invented, the only source of blood in emergency cases was relatives or friends of the patient—usually a very unsatisfactory and unreliable method of obtaining a supply. In a series of 43 maternal deaths from postpartum hæmorrhage in the Glasgow Maternity Hospital during the decade 1925–34, blood-transfusion was given only twice (Baird 1936). Since 1948, regional blood-transfusion services have been perfected. Blood has become much more widely available and standards of asepsis and of typing of blood have been raised. Despite these advances, antepartum and postpartum hæmorrhage are still very much dreaded by midwives and doctors, since even under the best conditions there are occasional fatalities.

Toxæmia

So little progress had been made in preventing deaths from eclamptic toxæmia before 1939 that many entertained serious doubts as to the value of antenatal care in the prevention of eclampsia. It is worth remembering, however, that in the Maternity Services (Scotland) Act of 1937, it was laid down, for the purpose of calculating the remuneration of the doctor, that three antenatal examinations should be carried out. This was taken by some doctors as the optimum rather than the minimum, which makes it scarcely surprising that the benefits derived from antenatal care conducted on these lines were disappointing. Bearing in mind that no specific cure for pre-eclampsia has yet been discovered, the gradual but steady fall in the death-rate since 1941 must be regarded as satisfactory. To minimise the damage done by the disease we have to rely on a high and steadily improving standard of antenatal care. This means very frequent examinations and sometimes long-continued treatment in hospital, all very costly in time and money. Nevertheless, these methods when applied conscientiously have almost abolished deaths from eclampsia and pre-eclampsia and have greatly decreased the stillbirth-rate in these conditions.

Associated Conditions

Maternal deaths due to general medical or surgical conditions complicating pregnancy, especially heart-disease, used to be common; in addition, many deaths caused by such obstetrical abnormalities as toxæmia, prolonged labour, and hæmorrhage were predisposed to by poor maternal health and physique.

Another striking feature of those days was the large number of deaths associated with excessive childbearing. In the Glasgow Maternity Hospital in 1925–34 out of 999 maternal deaths, 227 (27%) were in women who had previously given birth to at least six children, and in about 100 cases (about 10% of all deaths in the hospital) the past obstetrical or medical history was so abnormal that further pregnancy should have been avoided at all costs (Baird 1936).

The report on a Confidential Enquiry on 1094 Maternal Deaths occurring in England and Wales in 1925–54 (Wrigley 1957) showed that toxæmia had become the most important single cause of death. The overall maternal mortality had fallen to about one-sixth of that of 1932; nevertheless, a primary avoidable factor was present in not less than 43% of cases. 10% of the women who died of toxæmia had not made any arrangements for antenatal care or confinement. Characteristically, these were elderly multiparæ, in whom the mortality from all causes is well above average. The most important single avoidable factor was the patient's failure to consult a doctor. Of the 1094 deaths, 153 (14%) followed abortion; and in 58 of these the abortion was known to have been procured by the mother herself. The majority of abortions were in married women whose circumstances were

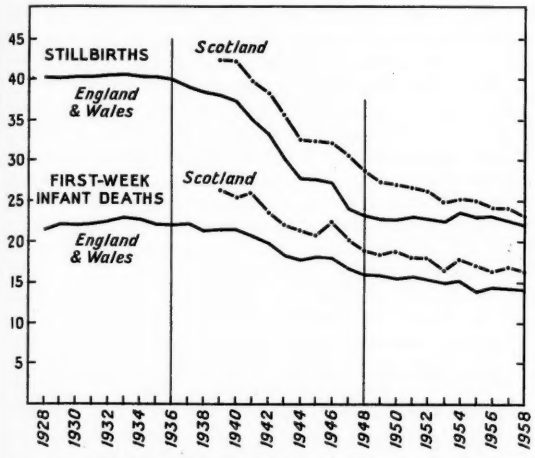


Fig. 1—Stillbirth and first-week infant death-rates. England and Wales 1928–58, Scotland 1935–58.

described as poor. Wrigley thought that these women "might have had a struggle to keep a home together and acted in the belief that they could not contemplate another addition to the family".

For every death from procured abortion, large numbers of other women go through a dangerous illness from which they may never fully recover. As Wrigley says, "the problem is just as much a social problem as it is medical, but it is one which will have to be tackled sooner or later all over the world".

Since Wrigley's report was published, maternal mortality has continued to fall and we are now able to say that, with a high standard of obstetric care and conscientious and cooperative patients, there should be few maternal deaths. But it would be a mistake to conclude that in the present state of knowledge they can be eliminated. In Britain, at least, deaths still occur very occasionally even under the best conditions, especially as a result of eclampsia and hæmorrhage.

Fœtal Mortality

Now that maternal mortality is so low, the death-rate amongst babies is regarded as a more satisfactory and more sensitive index of the efficiency of maternity services. The term perinatal mortality, defined as the number of stillbirths and deaths in the first week after birth per 1000 total births, is being used more and more in this connection. It is, of course, true that a few babies die from obstetrical causes after the end of the first week (notably from malformations), and a few during the first week from diseases acquired after birth (notably infections). I shall use the stillbirth-rate in discussing certain aspects of fœtal wastage. But, on the whole, the perinatal mortality-rate gives a more convenient and comprehensive measure of the wastage of babies from causes associated with childbearing. The lack of improvement in our perinatal mortality rate since 1948 is particularly disappointing since it has coincided in time with the first ten years of the National Health Service.

Since 1935 in Scotland the rate of improvement in the stillbirth and the first-week death-rate has been much slower than that for maternal mortality and the post-neonatal mortality. As already explained, the main causes of maternal mortality were amenable to direct treatment, and advances in treatment such as the introduction of the antibiotics have achieved spectacular results. By contrast, the unborn baby depends for its wellbeing mainly on the efficiency of the mother's reproductive system; although it fares remarkably well in times of privation, the obstetrician can at present do relatively little during the antenatal period to prevent such major causes of death as prematurity and what must, for want of a better term, be called "placental insufficiency".

Variations in the stillbirth-rate over the last thirty years will repay detailed study. Fig. 1 shows that in England and Wales between 1928 and 1933 it rose slightly, although during this period the maternity services were expanding. The fact that unemployment was rising and reached its peak of 21·5% of the insured population in 1932 is probably significant. After 1933 the stillbirth-rate began to fall, coinciding with a fall in unemployment. The rate of fall accelerated during the war years, when an enlightened food policy ensured adequate supplies of "protective" foods and vitamins for expectant and nursing mothers. The fact that expectant mothers were treated as a priority group gave wide publicity not only to the importance of good nutrition during pregnancy but also to the need for good antenatal care. The fall in the stillbirth-rate continued till 1948, with a temporary halt in 1945 and 1946. Since 1948 there has been practically no change.

The variations in the first-week death-rate in England and Wales have resembled those of the stillbirth-rate but have been less in degree. The patterns in Scotland have been similar except that the stillbirth-rate continued to fall slowly after 1948 and has now almost caught up with the English figure.

Further evidence of the importance of the standard of living can be adduced by comparing trends in regions of England and Wales having different socioeconomic characteristics. Fig. 2 shows that the stillbirth-rate rose

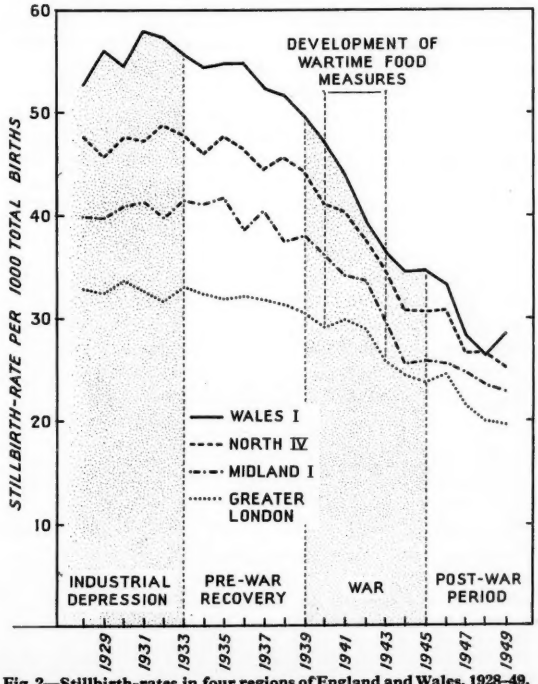


Fig. 2—Stillbirth-rates in four regions of England and Wales, 1928–49. (*By courtesy of the* Journal of Obstetrics and Gynæcology.)

appreciably in the two areas suffering most during the industrial depression of 1930–31—namely, Wales I and North IV—whereas there was only a small rise in London. During the pre-war recovery period the greatest fall took place in Wales. With the onset of war there was an immediate acceleration of the decline in the stillbirth-rate in Wales I and in North IV, while, by contrast, there was a slight increase in 1941 in London, followed by a lesser fall. By the end of the war, the gap in the stillbirth-rates between the areas had greatly narrowed, which is what one would expect from the fact that war-time food policy raised the standards of diets most in the areas where it was worst before the war.

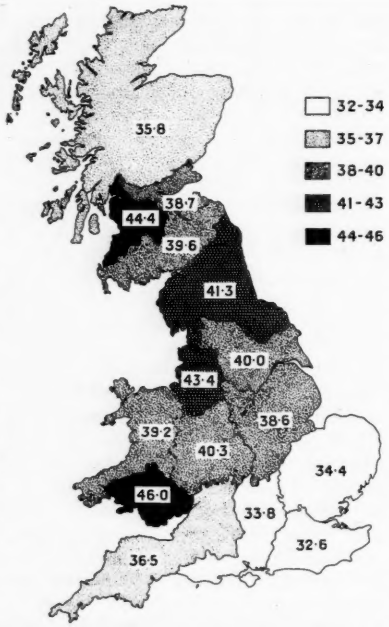


Fig. 3—Perinatal-mortality rates. Standard regions of England, Wales, and Scotland 1957.

The war-time fall in the stillbirth-rate suggests strongly that the quality of the diet consumed during pregnancy has an important influence on the outcome of pregnancy (Duncan, Baird, and Thomson 1952). Some may feel that this conclusion should be tested directly by means of a controlled feeding experiment, but the difficulties of such a test make it impracticable. If a change in mortality comparable to that achieved by the war-time food policy was to be expected, it would be necessary to use more than 5000 experimental subjects and a similar number of controls (Thomson 1959).

Fig. 3 shows that in 1957 there were still considerable differences in perinatal mortality in different parts of Britain. The regional differences are very similar to those for infant mortality, deaths from pulmonary tuberculosis, or deaths from any other disease associated with malnutrition and poor living conditions.

Health and Physique

Why do these regional differences in perinatal mortality still persist? We have produced much evidence to show that perinatal mortality is greatly affected by the health and physique of the mother as well as by her diet during pregnancy: in other words, the diet consumed from birth to maturity is at least as important as the diet taken during pregnancy (Thomson 1957).

The variations in health and nutrition which exist in Britain today are difficult to define and diagnose clinically; consequently we have used such indirect indices as social class and height. It is known that the percentage of short women increases steadily with declining social status, and in each social class tall women have lower perinatal death-rates and prematurity-rates than short women. For example, in Aberdeen the percentage of primigravidæ who are 5 ft. 4 in. or more in height declines from 46 in social classes I and II to 21 in classes IV and V, and the percentages under 5 ft. 1 in. are 9 and 28 respectively.

Fig. 4 indicates the remarkable changes produced in prematurity- and perinatal-mortality rates by social class and height. The prematurity-rate varies from 3·8% in tall women in social classes I and II to 14·3% in short women in classes IV and V. The perinatal-mortality rate rises in exactly the same way, ranging from 14·5 per 1000 in tall primigravidæ in the upper social classes to 55 per 1000 in short primigravidæ in the lowest social classes.

These facts, backed by much more evidence which we have amassed, suggest that many women in Aberdeen and probably in Britain as a whole, are short, not for genetic reasons, but because they are physically stunted and physiologically inefficient. Indeed, a simple guide to the general level of health of the women in a community can be obtained by measuring heights and constructing a distribution curve from the data. The variation in reproductive efficiency resulting from variations in maternal physique and health helps to explain some of the epidemiological facts. For example, it explains why in rural areas the perinatal mortality is often less than in the cities, despite much simpler maternity services.

The effect of the interplay of these two fundamental factors—namely, the health and physique of the patient and the standard of obstetric care—can be observed in many different situations. For example, in 1956 when the stillbirth-rate in Denmark was 17, it was 15 in Copenhagen, 17 in the other towns, and 18 in the rural areas of Jutland. Kaern (1958) has shown that in the rural areas, although the prematurity-rate was low (5%) the stillbirth-rate was relatively high, because the scarcity of obstetricians and maternity hospitals in these areas resulted in the death of babies from birth trauma and asphyxia which could have been avoided by a better standard of care in labour. In Copenhagen, on the other hand, although the prematurity-rate was higher than in the rural areas (7%), birth trauma and asphyxia were less frequent causes of death, because of a very high

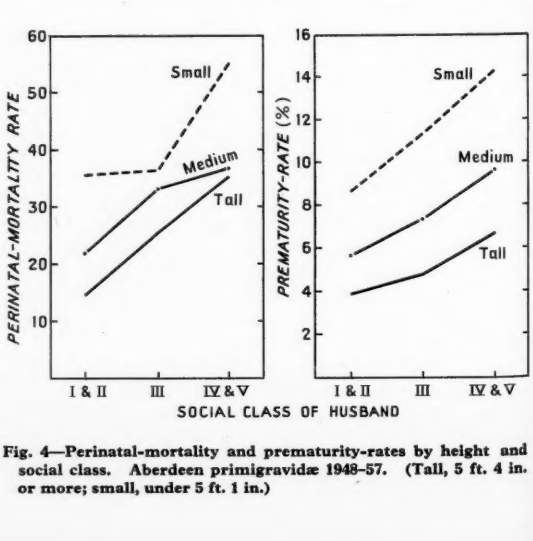


Fig. 4—Perinatal-mortality and prematurity-rates by height and social class. Aberdeen primigravidæ 1948–57. (Tall, 5 ft. 4 in. or more; small, under 5 ft. 1 in.)

standard of care in labour, and thus the very low stillbirth-rate of 15 was achieved.

The stillbirth-rate in Denmark generally, and in Copenhagen in particular, is very low by British standards and could not be attained without a very high level of health of the whole population. Some idea of this is obtained by the observation of Brandstrup (1958) that 67% of the women attending his obstetric clinic in Copenhagen measured 160 cm. (5 ft. 4 in.) or more in height; this is in striking contrast to the rate of 24% for Aberdeen primigravidæ.

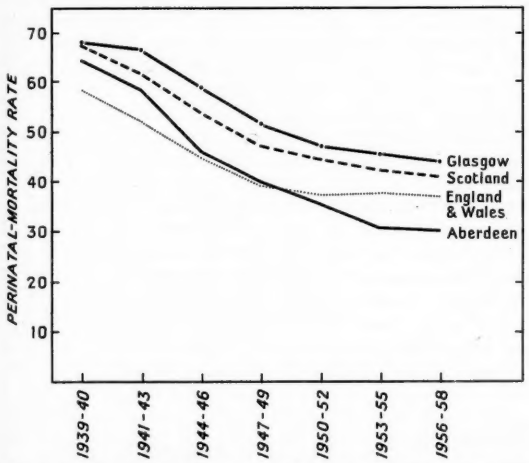


Fig. 5—Perinatal-mortality rates. England and Wales, Scotland, Glasgow and Aberdeen; 1939–58.

Other evidence of the superior physique of the Danes is available. Boyne and Leitch (1954) showed that the average height of young Servicemen in Denmark is now 174·4 cm. (5 ft. $8^1/_2$ in.) which is equivalent to that of young men in Britain coming from social classes I and II. The average increase in height in Denmark between 1915 and 1956 was about $2^1/_4$ in. (5·4 cm.).

There are no satisfactory observations of secular change in adult stature in Britain, but the increased rate of growth and in standard of health of schoolchildren, which is now occurring, should lead to an increase in the average stature of young adults. When the present generation of children constitutes the majority of mothers, the perinatal mortality should decline.

Standard of Care

We must, however, consider whether it is possible to lower perinatal mortality in the intervening years by improved standards of maternity care. At first glance, the stationary perinatal-mortality rate in the past ten years suggests that little is possible. It is highest in the heavily industrialised areas where the general level of health and physique is poor, which suggests that this factor imposes very definite limits to what can be done quickly. But our experience in Aberdeen, where the overall standard of health, as judged by the average height of the women, is by no means high, suggests that many infant lives could be saved now by improved organisation of maternity services and a higher standard of care.

Fig. 5 shows that the perinatal mortality in Aberdeen, which was appreciably higher than that for England and Wales before the war, has fallen considerably in the past ten years and is now about 20% less than that for England and Wales, 29% less than Scotland as a whole, and 37% less than Glasgow. It seems reasonable to postulate that what has been done in one area and no doubt in several others could be done to a greater or lesser extent in the country as a whole. To obtain further evidence on this point, the Aberdeen experience may be examined in more detail. The perinatal mortality in Aberdeen fell from 45 in 1948 to 28 in 1958. In view of the small number of cases involved it is not possible to analyse the changes year by year; consequently two five-year periods, 1948–52 and 1953–57, have been used for further study of the decline over the ten-year period.

Fig. 6 shows that the rate fell in first, second, and third pregnancies but not in fourth and subsequent pregnancies. The improvement was greatest in primigravidæ, especially in those aged 30 or over, with the result that the well-known rise in perinatal mortality with age has now disappeared. This reduction in mortality has, we believe, followed directly the application of the conclusions of our epidemiological and laboratory research into the causes of perinatal deaths. For example, we found that the risks of death from birth trauma, asphyxia, and placental insufficiency, rise steadily with increasing age, particularly in primigravidæ. This is especially true if the pregnancy lasts longer than 40 weeks. Fortunately a high proportion of these "elderly" primigravidæ belong to the upper social classes and are tall and healthy, and consequently the risk of prematurity is small. The main problem is to secure the safe delivery of the mature fœtus. The fall in the perinatal mortality has been least in those under 25 years of age. Many women, especially in the youngest age-group, come from social classes IV and V, where prematurity and malformations, especially of the central nervous system, are common. It must be noted, however, that in this age-group the full-time fœtus rarely dies from asphyxia, and the danger of prolonged pregnancy is slight, suggesting that some aspects of uteroplacental function are more dependent on the age of the patient than on her physique and general level of health. Again, prolonged labour from uterine dysfunction is seldom seen in very young primigravidæ unless there is underlying disproportion; consequently birth trauma is not an

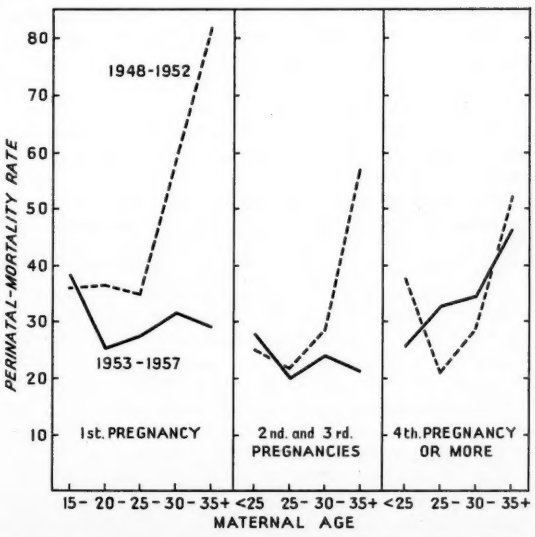


Fig. 6—Perinatal mortality by age and parity. Aberdeen 1948–57.

important cause of perinatal mortality at this age. The main problem in this group is clearly to improve the general health and physique.

The women in the higher parity groups, amongst whom the perinatal mortality has not fallen, come largely from the lower social classes, and consequently prematurity is an important cause of death. In addition, laxity of the abdominal wall predisposes to malposition and such conditions as prolapse of the cord. Increasing age, malnutrition, and hypertension also predispose to intrauterine death. Other factors to be taken into account in explaining our failure to reduce the perinatal mortality in this group are that the women often do not seek medical advice till

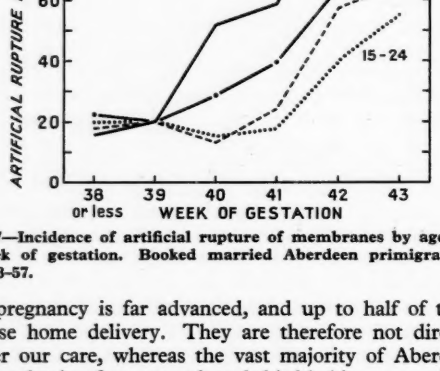


Fig. 7—Incidence of artificial rupture of membranes by age and week of gestation. Booked married Aberdeen primigravidæ: 1953–57.

the pregnancy is far advanced, and up to half of them choose home delivery. They are therefore not directly under our care, whereas the vast majority of Aberdeen women having first, second, and third babies are confined in hospital.

Our investigations suggested that there is much to be said for induction of labour to avoid the risk of placental insufficiency, which increases with prolonged pregnancy, and for a more liberal use of cæsarean section to avoid undue stress to the baby in labour. Fig. 7 gives the incidence of surgical induction of labour in primigravidæ in 1953–57. It shows that in the age-group 35+ induction was performed in all those who had reached the 42nd week of pregnancy and in 55% of those reaching the 41st week; the younger the woman the lower the percentage having induction at each week of gestation. The cæsarean-section rate in primigravidæ increased from 2·8% in 1948–52 to 4·6% in 1953–57.

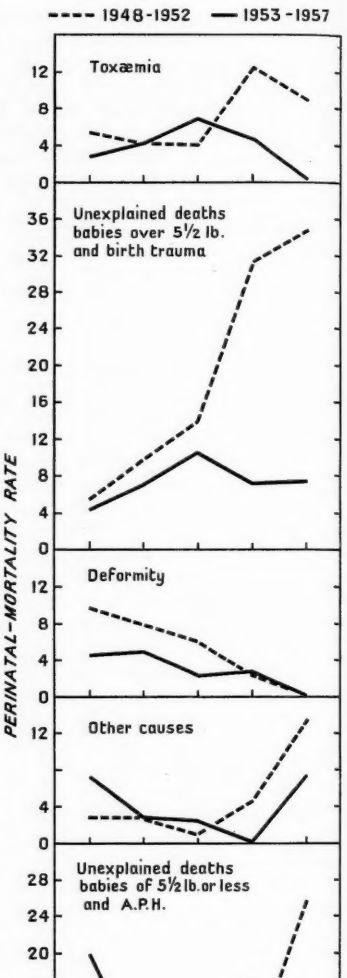
The table gives an analysis of cæsarean-section and perinatal-mortality rates in primigravidæ, by the age and height of the mother, in 1953–57. The cæsarean-section rate rises from 2·1% in tall women to 8·8% in short women, and from 2·2% in the age-group 15–19 to 32% in those aged 35 or more. Tall women between the ages of 25–29 and 30–34 have the lowest perinatal mortality (about 10 per 1000), which is one-third of the average for all primigravidæ. To secure these very low death-rates, however, cæsarean-section rates of 2·2 and 6·3% respectively in the two age-groups were considered necessary, most often because of prolonged labour due to uterine dysfunction or because of fœtal distress. In the age-group 20–24, the perinatal mortality was higher (21 per 1000), but here the cæsarean-section rate was very low (0·5%), because in this group, as already stated, prolonged labour and placental insufficiency are uncommon, although the adverse social factors result in a higher perinatal mortality from prematurity, antepartum hæmorrhage, and malformation of the central nervous system—deaths which obviously cannot be prevented by increased use of cæsarean section. In the age-group 15–19, where the perinatal mortality is 40 per 1000, the adverse social factors are even more important.

EFFECT OF MATERNAL AGE AND HEIGHT ON CÆSAREAN-SECTION AND PERINATAL-MORTALITY RATES

Booked Aberdeen primigravidæ, single births, 1953–57

Age	15–19	20–24	25–29	30–34	35+	All ages
Tall (5 ft. 4 in. and over)	0·8 *41*	0·5 *21*	2·2 *11*	6·3 *8*	17·1 *29*	2·1 *18*
Medium	0·7 *34*	2·0 *27*	5·1 *30*	14·0 *29*	31·9 *21*	4·0 *29*
Small (under 5 ft. 1 in.)	5·7 *52*	5·2 *27*	13·4 *45*	16·4 *18*	61·1 *0*	8·8 *34*
All heights	2·2 *41*	2·4 *26*	5·8 *26*	11·6 *20*	32·0 *20*	4·6 *27*

Perinatal-mortality rates = italic figures.



ig. 8—Perinatal-mortality rates by clinical cause and maternal age. All Aberdeen primigravidæ 1948–52 and 1953–57.

At all heights the cæsarean-section rate rises sharply in women of 35 years or more. Even in tall women it rises from 6% in the age-group 30–34 to 17% in the 35+ age-group. This is because, after the age of 35, deterioration of uterine and placental function, even in women of excellent health and physique, is so frequent, and the

need to secure a live baby so great, that cæsarean section is performed if the baby is thought to be in any danger.

Fig. 8 shows that the most striking change between the first and the second five-year period is the reduction in unexplained and asphyxial deaths and those from birth trauma, especially in primigravidæ aged 30 or more. It is of some interest to note that the death-rate from these causes is now greatest in the age-group 25–29. This is explained by the fact that these women are sufficiently old for the increased risks of uterine and placental insufficiency to exist, but young enough to make one hesitate to employ induction and cæsarean section as freely as in the older women. There is also a substantial fall in the death-rate from toxæmia in the older women. The mortality associated with prematurity and antepartum hæmorrhage has not fallen. We cannot take any credit for the fall in the incidence of deaths from malformations especially in younger primigravidæ, which was presumably due to chance.

The extent of the increased operative intervention which has been thought necessary to give these results is as follows. In primigravidæ aged 30 years or more the incidence of artificial rupture of the membranes increased from 13 to 35% and the cæsarean-section rate from 12 to 16%. This resulted in a reduction in the perinatal mortality from birth trauma, asphyxia and unexplained death of the full-time fœtus from approximately 27 to 10 per 1000. In the younger age-groups, the return in terms of a lowering of perinatal mortality was much less. Nevertheless, since a large proportion of primigravidæ are under the age of 25 (about 65%), the effect of a slight improvement in mortality in this age-group on the *overall perinatal-mortality rate* in primigravidæ is as great as a very much bigger reduction in mortality in the 10% of primigravidæ who are over 30.

Unfortunately surgical induction by rupture of the membranes increases the risk of infection, especially when labour does not follow the induction quickly; and occasionally a cæsarean section has to be done because labour fails to start despite every effort. There is no doubt also that, if the first child is delivered by cæsarean section, the second child is likely to be delivered by the same method. In addition, a cæsarean section performed in a first labour seems to act as a slight deterrent to future childbearing. Since the increased use of surgical induction and cæsarean section has undoubtedly saved infant lives, these drawbacks are not in themselves good reasons for discontinuing the method, unless it can be shown that the risk to the mother is thereby increased.

Between 1948 and 1957, 1665 cæsarean sections were performed in the Aberdeen Maternity Hospital with five maternal deaths. This rate, 0·3%, is of course much higher than the overall maternal mortality, but it must be remembered that the alternative to cæsarean section would often be a further prolongation of labour and a difficult forceps delivery. In fact, 3 of the 5 deaths occurred in cases where labour had lasted more than forty-eight hours and where the operation was performed because of maternal distress and not primarily to save the baby. Antibiotics and improved methods of treating shock and hæmorrhage would no doubt make vaginal delivery in such cases much safer than it was twenty years ago. A precise and up-to-date estimate of the risk cannot be given, since very few difficult vaginal deliveries after prolonged labour are now undertaken; but even if the maternal death-rate were low the incidence of morbidity would undoubtedly be high. The effect of avoiding damaging vaginal deliveries can be assessed from the fact that young women with extensive damage to the cervix, vagina, rectum, and bladder are seldom, if ever, seen nowadays in a gynæcological department.

Similarly, in considering the effect of difficult delivery on the baby, we have to assess, in addition to the immediate mortality, the risk of permanent damage in those who survive. Not surprisingly, the measures introduced in 1953–57, which have been so successful in preventing deaths from birth trauma and asphyxia, have also decreased the overall incidence and severity of asphyxia and have made resuscitation easier. It is important, however, to know whether the few born asphyxiated suffer any permanent damage as a result, since, if they do, still further efforts to avoid asphyxia at birth will be required. Recently Fraser and Wilks (1959) followed up, at the age of $7^1/_2$ years, a group of children who, born in 1948–50, had been severely asphyxiated at birth: these were carefully matched against a control group of babies born in excellent condition. Very little difference in the incidence of physical lesions or psychological disturbances in the two groups was found. These negative findings are most reassuring.

The *British Medical Journal* (1958), noting that there is at present no adequate method of assessing placental function, has said: "The obstetrician still has to rely on his clinical judgment in deciding afresh in each case whether induction of labour will be of benefit to the baby's health or not." In our experience, if the obstetrician relies entirely on his judgment of the individual case he will lose the occasional baby because "placental insufficiency" cannot be diagnosed reliably. The alternative is to perform numerous routine inductions of labour on the basis of epidemiological inference, and to use cæsarean section freely in the interests of the baby. On balance, we think that this policy has been justified in the absence of any more selective method of prevention. There is, of course, considerable difference of opinion in obstetrical circles about the dangers of prolonged pregnancy and the methods of avoiding them. It may be that the regime we have used is unnecessary and that just as good results can be obtained by a more conservative approach; but statistically sound evidence in support of conservatism has not so far been published in Britain. Figures for the City of Aberdeen have been given in some detail to illustrate the necessity for accurate statistical analyses of all the relevant facts if reliable conclusions are to be drawn about any method of treatment.

Conclusions on Perinatal Mortality

There is evidence that by improving the standard of the maternity services, the present perinatal-mortality rate of 36 in England and Wales and 39 in Scotland could be lowered to about 30 per 1000. In some areas, where the general level of health is good, it could be reduced below 30; but in the heavily industrialised areas this level might not be reached.

To reduce the national perinatal mortality much below 30 per 1000 would require a considerable improvement in the general level of health and physique. As schoolchildren have become taller and healthier in recent years, the outlook is hopeful. Earlier marriage, which is such a striking feature of post-war Britain, must make childbearing easier and safer, especially when accompanied by higher standards of health and physique. The tendency to avoid excessive childbearing, and especially if it is

continued till after the age of 35, will also reduce the risks. In time it should be possible to keep the national perinatal mortality to about 25 per 1000 with less difficulty than we experience in keeping the present rate at 36.

REFERENCES

Baird, D. (1936) *Lancet*, i, 295.
Boyne, A. W., Leitch, I. (1954) *Nutr. Abstr. Rev.* **24**, 255.
Brandstrup, E. (1958) Personal communication.
British Medical Journal (1958) i, 1226.
Duncan, E. H. L., Baird, D., Thomson, A. M. (1952) *J. Obstet. Gyn. Brit. Emp.* **59**, 183.
Fraser, M. S., Wilks, J. (1959) *ibid.* **66**, 748.
Kaern, T. (1958) Personal communication.
Porter, I. A. (1958) Alexander Gordon, M.D., of Aberdeen. Aberdeen University Studies no. 139. Edinburgh.
Thomson, A. M. (1957) *Proc. Nutr. Soc.* **16**, 45.
— (1959) *Brit. J. Nutr.* **13**, 509.
Wrigley, A. J. (1957) *S. Afr. med. J.* Oct. 19, p. 1057.

(To be concluded)

BACTERIOLOGICAL STUDIES ON A NEW PENICILLIN—BRL.1241

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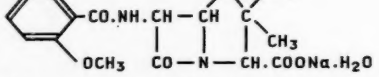
BRL.1241 is a new penicillin prepared from 6-amino-penicillanic acid.* Unlike penicillin G and V, this penicillin is stable to staphylococcal penicillinase and is active against the penicillinase-producing penicillin-resistant staphylococci.

Investigation

The compound is sodium 6-(2:6-dimethoxybenzamido) penicillanate monohydrate, with the structural formula:



It is a white crystalline solid, extremely soluble in water giving a clear neutral solution. In neutral solution about 50% of the activity is lost in 5 days at room temperature. In a refrigerator at 5°C, neutral solutions lose about 20% of the activity in 5 days. BRL.1241 is unstable in acid solution. At pH 2·0 at 25°C, 50% of the activity is lost in 20 minutes.

Bacteriological Methods

Minimum inhibitory concentrations required to prevent growth for 24 hours at 37°C were determined by serial dilution in nutrient broth ('Oxoid' no. 2) and also in nutrient agar ('Oxoid' no. 2). A concentration of 5% whole blood was incorporated in the media for the streptococci and pneumococci. Serial dilution tests were normally inoculated with one drop of an overnight broth culture. Serial dilutions in agar were poured into petri dishes and inoculated by streaking a loop from an overnight broth culture. The effect of BRL.1241 on bacterial growth in broth was also measured by opacity readings in a 'Unicam' SP.600. Sensitivity of test organisms to antibiotics other than BRL.1241 and penicillin G was determined using 'Oxoid multodisks'. Viable counts were made by preparing 10-fold dilutions in agar and colony counting. In addition to viable counts, an assessment of bactericidal activity was also obtained by making a streak approximately 3 cm. long on agar using a loop from each tube of a serial dilution in broth. Where the resulting growth of such streaks consisted of relatively few isolated colonies the number of colonies was recorded.

Tolerance to BRL.1241, and the rate at which tolerance developed on exposure to BRL.1241, was determined by daily transfer from serial dilutions in broth using as inoculum for the next series the tube with the highest concentration of BRL.1241 permitting growth.

Penicillinase

Studies were made using penicillinase produced by *Bacillus cereus* 569/H (N.C.T.C.9945) and also the penicillinase produced by a culture of *Staphylococcus pyogenes* BRL.1083. *B. cereus* was grown overnight in shaken flasks at 37°C and the cell-free culture fluid used as enzyme. A suitable dilution of this enzyme was made as required. *Staph. pyogenes* BRL.1083 was grown in nutrient broth in shaken flasks at 37°C for 6 hours and BRL.1241 (0·5 μg. per ml.) was added as an inducer of penicillinase formation. Incubation was then continued overnight, and the whole culture, including the cells, was used as enzyme. BRL.1241 was used as an inducer because it is stable to penicillinase and is more effective than penicillin G or V.

Results

Minimum Inhibitory Concentrations

The minimum concentrations required to inhibit growth of bacteria (M.I.C.) for 24 hours at 37°C are shown in table I. The penicillin-resistant staphylococci in this table were both resistant to penicillin G, 125 μg. per ml., in this type of test. Like penicillin G and V, BRL.1241 is active chiefly against the gram-positive bacteria and such gram-negative bacteria as *Neisseria catarrhalis*. The compound shows very little activity against the gram-negative bacilli. Activity against the staphylococci is independent of resistance to penicillin G, the highly resistant strains showing the same order of sensitivity to BRL.1241 as the penicillin-sensitive strains.

Activity of BRL.1241 against a wider range of penicillin-resistant staphylococci is shown in table II. All the cultures were coagulase-positive cultures of *Staph. pyogenes* recently isolated in hospitals. Most of them

TABLE I—MINIMUM INHIBITORY CONCENTRATIONS OF BRL.1241 FOR GROWTH OF BACTERIA
Cultures incubated for 24 hours

Species	Strain	M.I.C. (μg. per ml.)	
		Serial dilution in agar	Serial dilution in broth
Escherichia coli	BRL.1008	>250	..
Proteus vulgaris	NCTC 401	>250	..
Salmonella typhi	NCTC 8393	>250	>250
S. typhimurium	BRL.1076	125	..
Shigella shigæ	NCTC 4837	250	..
Aerobacter aerogenes	NCTC 418	>250	..
Pseudomonas pyocyanea	BRL.1058	>250	..
Neisseria catarrhalis	NCTC 3622	0·25	..
Sarcina lutea	NCTC 8553	0·025	..
Diplococcus pneumoniæ	BRL.1221	0·05	0·06
" "	BRL.1223	0·05	..
" "	BRL.1224	0·5	..
" "	NCTC 7465	0·25	..
Streptococcus pyogenes β type	BRL.1230	0·5	0·5
" " " "	BRL.1231	0·05	..
" " " "	BRL.1275	0·05	..
" " " "	BRL.1320	0·25	..
" " " "	BRL.1321	0·06	..
Strep. viridans	BRL.1246	0·12	0·25
" "	NCTC 779	0·12	..
" "	BRL.1323	0·12	..
" "	BRL.1326	0·6	..
" "	NCTC 3165	0·25	..
Strep. faecalis	BRL.1207	50·0	..
Corynebacterium hofmanni	NCTC 8338	0·6	0·12
Staphylococci, penicillin-sensitive:			
Oxford staphylococcus	BRL.1227	1·25	1·25
Staph. pyogenes	NCIB 8588	1·25	..
" "	BRL.1270	2·5	..
" "	BRL.1402	1·25	..
" "	BRL.1408	1·25	..
Staphylococci, penicillin-resistant:			
Staph. pyogenes	BRL.1083	2·5	2·5
" "	BRL.1089	2·5	2·5

* Beecham Research Laboratories' trade name for BRL.1241 is 'Celbenin'.

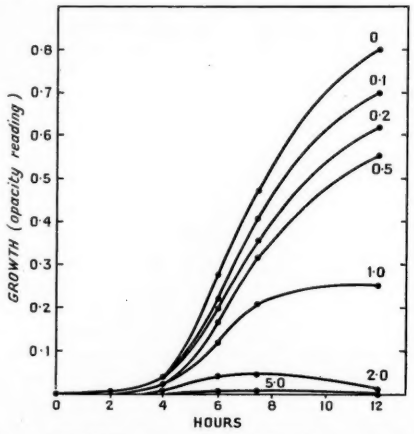
TABLE II—MINIMUM INHIBITORY CONCENTRATIONS OF BRL.1241 FOR GROWTH OF PENICILLIN-RESISTANT STAPHYLOCOCCI
(Serial dilutions in agar)

Culture	Phage-type	Resistance pattern *						M.I.C. (μg. per ml.)	
		C	E	N	O	S	T	Penicillin G	BRL.1241
Staph. aureus (Oxford)	..	−	−	−	−	−	−	0·02	1·25
Staph. pyogenes BRL.1083	No known type	+	+	−	+	++	++	125·0	2·5
„ „ BRL.1089	80	−	−	..	−	++	++	125·0	2·5
„ „ BRL.1112	..	+	−	−	+	++	++	125·0	1·25
„ „ BRL.1113	..	−	−	−	−	++	++	125·0	1·25
„ „ BRL.1105	..	−	−	−	−	++	++	125·0	2·5
„ „ BRL.1091	80	−	−	..	−	++	++	62·5	2·5
„ „ BRL.1111	80	+	−	−	+	++	−	50·0	2·5
„ „ BRL.1093	54+	−	+	..	+	++	++	50·0	2·5
„ „ BRL.1094	54+	−	+	..	+	++	++	50·0	2·5
„ „ BRL.1095	80	−	−	..	−	++	−	25·0	2·5
„ „ BRL.1099	80	+	−	−	+	++	++	12·5	2·5
„ „ BRL.1104	..	++	++	++	++	++	++	12·5	2·5
„ „ BRL.1090	79/53/54/77	+	−	−	+	−	−	10·0	2·5
„ „ BRL.1098	80	+	−	−	−	++	++	5·0	2·5
„ „ BRL.1096	80	+	−	−	+	++	++	5·0	1·25
„ „ BRL.1097	80	+	−	−	−	++	++	5·0	2·5
„ „ BRL.1100	80	−	−	−	−	++	++	5·0	2·5
„ „ BRL.1101	80	+	−	−	−	−	++	5·0	2·5
„ „ BRL.1102	80	+	−	−	+	++	−	5·0	2·5
„ „ BRL.1085	58/80	−	−	−	−	−	−	2·5	1·25
„ „ BRL.1108	..	−	−	−	+	−	−	2·5	1·25
„ „ BRL.1084	42E	+	+	+	+	−	−	1·25	1·25

* C = chloramphenicol 10 μg. E = erythromycin 10 μg. − denotes sensitive
N = novobiocin 5 μg. O = oleandomycin 5 μg. + denotes partially resistant
S = streptomycin 10 μg. T = tetracycline 10 μg. ++ denotes highly resistant

were phage-type 80 and resistant to one or more antibiotics as well as to penicillin. The results in table II show that activity of BRL.1241 is independent of resistance to other antibiotics as well as penicillin. All the strains were sensitive to BRL.1241 in concentrations of 1·25 to 2·5 μg. per ml. Resistance of these cultures to penicillin G ranged from 1·25 to 125 μg. per ml.

Growth curves for a penicillin-resistant culture of *Staph. pyogenes* BRL.1083, in broth culture with different



Effect of BRL.1241 on growth of *Staph. pyogenes* BRL.1083 (penicillin-resistant) in nutrient broth at 37°C. The figures on each curve indicate the concentration of BRL.1241 in μ.g per ml.

concentrations of BRL.1241 are shown in the figure. BRL.1241 was added at time 0 and 0·1 ml. of an overnight broth culture was used to inoculate 100 ml. of nutrient broth in 250 ml. shaken flasks which were incubated at 37°C. Growth was measured by opacity in the Unicam at 450 mμ. A concentration of 2·0 μg. per ml. almost completely prevented growth and a concentration of 1·0 μg. per ml. reduced growth to about 30% of the control.

Effect of Inoculum Size

With cultures of penicillin-resistant staphylococci, the M.I.C. with penicillin G is greatly affected by the size of the inoculum. The results in table III show that inoculum size has very little effect on the activity of BRL.1241. This would be expected, since BRL.1241 is not destroyed by staphylococcal penicillinase.

Bactericidal Activity

The bactericidal activity of BRL.1241 is shown in table IV.

Broth cultures of *Staph. pyogenes* BRL.1083 (penicillin-resistant) were incubated at 37°C for 3 hours, by which time a light growth was clearly visible. Compound BRL.1241 was then added in different concentrations and incubation continued. Viable counts were made at the time of addition of BRL.1241 and at intervals thereafter. A concentration of 2·5 μg. BRL.1241 per ml. reduced the viable count from 44 million cells per ml. to 123 cells in 30 hours and a concentration of 5·0 μg. per ml. reduced the viable count from 44 million cells per ml. to 90 cells in 5 hours.

Bactericidal activity was also assessed by streaking out on agar a loop from serial dilution cultures in broth. The broth cultures were carried out using plain nutrient broth and also broth containing 40% human serum. BRL.1241 was added to give serial dilutions and the broths inoculated with one drop of a 1/10 dilution of an overnight culture of the Oxford staphylococcus and also *Staph. pyogenes* cultures BRL.1083 and BRL.1093. Viable streaks of the broths made immediately after inoculation resulted in heavy confluent growth in the streaks. After incubation at 37°C overnight, the streaks were again

TABLE III—EFFECT OF INOCULUM SIZE ON THE ACTIVITY OF BRL.1241 IN SERIAL DILUTION IN BROTH

Inoculum	M.I.C. (μg. per ml.)	
	Oxford staph.	*Staph. pyogenes* BRL.1083 *
Overnight broth culture:		
1 drop	1·25	2·5
1 drop of dilution 1 in 100	0·6	2·5
1 drop of dilution 1 in 1000	0·6	1·25
1 drop of dilution 1 in 1,000,000 ..	0·5	1·25

* Penicillin-resistant.

TABLE IV—BACTERICIDAL ACTIVITY OF BRL.1241 AGAINST *Staph. pyogenes* BRL.1083 (PENICILLIN-RESISTANT)

BRL.1241 (μg. per ml.)	Viable counts (organisms per ml.)			
	0 hour	3 hours	5 hours	30 hours
0	44×10^6	148×10^9	$>100\times10^{11}$	$>100\times10^{11}$
2·5	..	100×10^4	189×10^3	123
5·0	..	60×10^2	90	4
10·0	..	76×10^2	58	0

TABLE V—BACTERICIDAL ACTIVITY OF BRL.1241 IN BROTH WITH AND WITHOUT THE PRESENCE OF HUMAN SERUM

Serial dilution broth cultures were inoculated with 1 drop of a 1-in-10 dilution of an overnight culture and incubated for 24 hours at 37°C. Viable streaks were then made on agar and the subsequent growth recorded

Staph. pyogenes BRL.1083 and BRL.1093 were both highly resistant to penicillin

BRL.1241 (μg. per ml.)	Oxford staph.		*Staph. pyogenes* BRL.1083		*Staph. pyogenes* BRL.1093	
	..	+40% serum	..	+40% serum	..	+40% serum
0·1	+++	+++	+++	+++	+++	+++
0·25	+++	+++	+++	+++	+++	+++
0·5	++	++	+++	+++	+++	+++
1·0	8	24	+++	+	+++	++
2·5	0	3	0	0	26	17
5·0	0	0	0	0	0	0
10·0	0	0	0	0	0	0

+++=heavy confluent growth
++ =light confluent growth
+ =semi-confluent growth
numbers=actual numbers of colonies in the streak.

made from each tube and the resulting growth recorded after incubation overnight. The results are shown in table V. With the Oxford staphylococcus a concentration of 1·0 μg. per ml. resulted in viable streaks showing only a very few colonies and the presence of 40% human serum did not significantly diminish this effect. With the cultures of penicillin-resistant *Staph. pyogenes* a concentration of 2·5 μg. per ml. resulted in none, or very few, colonies in the viable streaks, and again serum had no effect.

Thus, the compound appeared to be bactericidal at concentrations only very slightly higher than the minimum inhibitory concentrations.

Effect of Serum

Human serum does not diminish the activity of BRL.1241 either in liquid or in solid culture. The minimum inhibitory concentration of the compound in the presence of 40% human serum is the same as that in the absence of serum. Similarly, the bactericidal activity of BRL.1241 is not diminished by the presence of serum. The results shown in table V, which illustrate the bactericidal activity of BRL.1241, show that in the presence of 40% human serum the bactericidal activity is certainly not significantly less than it is in the absence of serum, and in certain of the experiments with the penicillin-resistant staphylococci it appeared to be even slightly greater.

BRL.1241 in Combination with Penicillin G

Experiments were carried out on the activity of mixtures of penicillin G and BRL.1241 in different proportions. The results showed no evidence of synergism, or antagonism, between the two antibiotics either against the Oxford staphylococcus or against cultures of penicillin-resistant staphylococci.

Resistance to BRL.1241

Prolonged incubation of serial dilution tests, both in broth and in agar, did not materially alter the M.I.C. of BRL.1241 against cultures of penicillin-resistant staphylococci. There was no evidence, therefore, that such cultures include resistant members of the population which are able to grow up after long periods. Experiments were also carried out with the surviving colonies which grew in viable streaks from broth cultures which had been incubated with concentrations of BRL.1241 which killed over 99·9% of the original populations. When tested against BRL.1241, these cultures showed the same sensitivity as did the original cultures and did not represent resistant strains. Among all the cultures of penicillin-resistant staphylococci tested, naturally occurring strains resistant to BRL.1241 were not encountered.

Tolerance to BRL.1241 does develop very slowly in vitro when cultures are repeatedly transferred in broth containing BRL.1241.

In the results shown in table VI, three strains of penicillin-resistant staphylococci were transferred daily in broth culture containing BRL.1241 as described under the heading of Investigation. In addition, the Oxford staphylococcus was also transferred in the same way in broth containing BRL.1241 and also in broth containing penicillin G. The M.I.C. for each of fifteen transfers was recorded. Tolerance to BRL.1241 developed only very slowly and not to a very great extent. Tolerance by the Oxford staphylococcus to penicillin G developed considerably quicker. After fifteen transfers the penicillin-resistant staphylococci showed a 5–10-fold increase in tolerance to BRL.1241, whereas after the same number of transfers the Oxford staphylococcus showed a 500-fold increase in tolerance to penicillin G. Those cultures which gained in tolerance to BRL.1241 as a result of repeated transfer in broth containing this compound did not lose any tolerance when subsequently taken through six transfers in plain broth. The same cultures also retained their coagulase-positive character and showed the same degree of resistance to penicillin G as did the original cultures. Estimation of penicillinase production showed no significant difference between cultures which had developed some tolerance to BRL.1241 and the original cultures. Growth of the BRL.1241-tolerant cultures, however, was significantly slower than the normal cultures.

TABLE VI—DEVELOPMENT OF TOLERANCE TO BRL.1241

Cultures were transferred daily from serial dilutions in broth, the last tube showing growth being used as inoculum for the next transfer

No. of transfers	M.I.C. (μg. per ml.)				
	Penicillin G Oxford staph.	BRL.1241			
		Oxford staph.	BRL.1083*	BRL.1093*	BRL.1089*
0	0·01	2·5	2·5	2·5	2·5
1	0·05	2·5	5·0	2·5	5·0
2	0·06	5·0	5·0	5·0	5·0
3	0·12	6·2	5·0	6·2	6·2
4	0·25	6·2	6·2	6·2	6·2
5	0·25	12·5	6·2	6·2	6·2
6	0·25	25·0	6·2	6·2	6·2
7	0·6	25·0	6·2	12·5	6·2
8	1·2	25·0	6·2	12·5	12·5
9	2·5	25·0	5·0	6·2	6·2
10	2·5	25·0	12·5	12·5	12·5
11	2·5	25·0	12·5	25·0	25·0
12	1·2	12·5	12·5	25·0	25·0
13	2·5	25·0	12·5	25·0	25·0
14	5·0	25·0	12·5	25·0	25·0
15	5·0	25·0	12·5	25·0	25·0

* Penicillin-resistant cultures of *Staph. pyogenes.*

TABLE VII—STABILITY OF BRL.1241 TOWARDS STAPHYLOCOCCAL PENICILLINASE

Staph. pyogenes BRL.1083 was grown in nutrient broth in the presence of 0·5 μg. BRL.1241 per ml. 5 ml. of the overnight culture was added to 5 ml. of phosphate buffer pH 6·0 containing penicillin G or BRL.1241 to give a final concentration of 1 mg. per ml. Enzyme reaction allowed to proceed at 37°C

Time (minutes)	Penicillin G (μg. per ml.)	BRL.1241 (μg. per ml.)
0	1000	1000
5	330	1000
10	0	1000
20	0	1000
40	0	1000
60	0	1000

Cross-resistance

Cross-resistance typically occurs between antibiotics having similar chemical structure. Since BRL.1241 is a penicillin, cross-resistance would not be expected with other antibiotics in common use, and the results in table II show that there is certainly no cross-resistance between BRL.1241 and chloramphenicol, erythromycin, novobiocin, oleandomycin, streptomycin, and tetracycline.

TABLE VIII—STABILITY OF BRL.1241 TOWARDS *B. cereus* PENICILLINASE

Overnight broth filtrate of *B. cereus* 569/H was used as enzyme. 2·0 ml. was added to 8·0 ml. of phosphate buffer pH 6·4 containing penicillin G or BRL.1241 to give a final concentration of 2 mg. per ml. Incubated at 37°C

Time (minutes)	Penicillin G (μg. per ml.)	BRL.1241 (μg. per ml.)
0	2000	2000
1	0	1740
2	0	1610
3	0	1500
4	0	1400
5	0	1330

Stability to Penicillinase

Using staphylococcal penicillinase prepared as described under Investigation, no inactivation of BRL.1241 could be demonstrated after 60 minutes' incubation. The same enzyme, under the same conditions, completely inactivated a solution containing 1 mg. penicillin G per ml. in 10 minutes. Stability of BRL.1241 to staphylococcal penicillinase was unaffected by pH. Results with staphylococcal penicillinase are shown in table VII.

Using *B. cereus* penicillinase, some inactivation of BRL.1241 took place but at a very much slower rate than with penicillin G. The pH optimum for *B. cereus* penicillinase and BRL.1241 is sharper and lower (6·2–6·4) than for penicillin G (6·5–7·0). Results for inactivation of BRL.1241 with *B. cereus* penicillinase are shown in table VIII. With *B. cereus* penicillinase there is an initial rate of inactivation which is faster than the subsequent rate. This may be due to a low rate of breakdown of enzyme-substrate complex. Preliminary studies on the kinetics of inactivation with *B. cereus* penicillinase indicate a K_m of approximately 0·5 mg. per ml.

BRL.1241 induces formation of penicillinase. Using a penicillinase-producing culture of *Staph. pyogenes* BRL.1083, the maximum induction occurred with a concentration causing significant inhibition of growth. When the inducer was added as described under Investigation, the optimum concentration was 0·5 μg. per ml.

Inactivation of penicillin G by staphylococcal penicillinase was found to be unaffected by the presence of BRL.1241. There was no evidence of competitive inhibition by BRL.1241 with staphylococcal penicillinase. With *B. cereus* penicillinase, on the other hand, BRL.1241 does competitively inhibit the inactivation of penicillin G. Equimolar concentrations of BRL.1241 and penicillin G show a rate of penicillin-G inactivation only 10% of that in the absence of BRL.1241.

Discussion

The outstanding property of this penicillin BRL.1241 is the stability to staphylococcal penicillinase and the resulting activity against the penicillin-resistant staphylococci. Cultures of staphylococci resistant to concentrations of penicillin G as high as 125 μg. per ml. are almost as sensitive to BRL.1241 as is the Oxford staphylococcus. Many of the penicillin-resistant staphylococci tested were phage-type 80, and all were sensitive to BRL.1241 at a concentration of 1·25–2·5 μg. per ml. These results have been confirmed by Elek and Fleming (1960), Knox (1960), Stewart et al. (1960) and Thompson et al. (1960). Penicillin BRL.1241 also shows the desirable properties of being bactericidal at concentrations only slightly higher than the minimum inhibitory concentrations and also of being unaffected by the presence of serum.

Although primarily of value because of its activity against penicillin-resistant staphylococci, BRL.1241 also shows relatively high activity against many other pyogenic gram-positive cocci. The cultures of β-hæmolytic streptococci tested showed a sensitivity of 0·05–0·25 μg. per ml. and the cultures of *Streptococcus viridans* of 0·12–0·6 μg. per ml. With cultures of *Diplococcus pneumoniæ* the M.I.C. was 0·05–0·5 μg. per ml. These results have been confirmed by Knox (1960) and Stewart et al. (1960). Against the gram-negative bacilli, BRL.1241 shows even less activity than penicillin G.

Naturally occurring strains of *Staph. pyogenes* resistant to BRL.1241 have not been encountered, and this has also been the finding of the other workers cited above. Development of tolerance in vitro, which does occur slowly, is of doubtful importance clinically, since this type of resistance to penicillin does not occur in vivo. Although tolerance to penicillin G can develop in vitro, the only penicillin-resistant staphylococci isolated clinically are those strains which are resistant because they produce penicillinase. This is not a character acquired as a result of exposure to penicillin: the penicillinase-producing strains are merely selected out by the presence of penicillin. Resistance to BRL.1241 comparable to that which exists to penicillin G would require the ability to inactivate BRL.1241 by a new penicillinase. Since cultures have not been encountered showing this property, it seems unlikely that the selection and proliferation of resistant strains will take place rapidly, if at all. In support of this it has been reported that resistant cultures have not been isolated after the clinical use of BRL.1241 (Elek and Fleming 1960, Stewart 1960).

Excluding the penicillin-resistant strains, BRL.1241 is not as active against *Staph. pyogenes* as is penicillin G or V. Activity is, however, of a similar order to that of many of the other antibiotics in current use, and adequate blood-levels are readily achieved (Knudsen and Rolinson 1960).

Summary

BRL.1241 is a new synthetic penicillin which is stable to staphylococcal penicillinase and active against penicillin-resistant staphylococci.

All the cultures of *Staphylococcus pyogenes* tested were sensitive to BRL.1241 in concentrations of 1·25–2·5 μg. per ml., regardless of their resistance to penicillin G and other antibiotics.

BRL.1241 is also active against other pyogenic gram-positive cocci including β-hæmolytic streptococci, *Streptococcus viridans*, and *Diplococcus pneumoniæ*.

BRL.1241 is bactericidal at concentrations only slightly higher than the minimum inhibitory concentrations, and activity is not diminished in the presence of serum.

Cultures of *Staph. pyogenes* became tolerant to BRL.1241 very slowly in vitro when subcultured in broth containing this antibiotic; but this does not seem to happen in vivo, and naturally occurring resistant strains have not been encountered.

Although stable to staphylococcal penicillinase, BRL.1241 is inactivated by *Bacillus cereus* penicillinase, but at a very much slower rate than penicillin G. BRL.1241 induces formation of penicillinase. With *B. cereus* penicillinase, BRL.1241 competitively inhibits inactivation of penicillin G, but this does not occur with staphylococcal penicillinase.

We are indebted to Dr. J. Farquharson, director of research, for his interest in the work, to Miss J. Guy and Miss E. Widden for technical assistance, and to the directors of Beecham Research Laboratories Limited for permission to publish.

REFERENCES

Elek, S. D., Fleming, P. C. (1960) *Lancet*, ii, 569.
Knox, R. (1960) *Brit. med. J.* ii, 690.
Knudsen, E. T., Rolinson, G. N. (1960) *ibid.* p. 700.
Stewart, G. T., Nixon, H. H., Coles, H. M. T. (1960) *ibid.* p. 703.
Thompson, R. E. M., Harding, J. W., Simon, R. D. (1960) *ibid.* p. 708.

CHEMOTHERAPEUTIC STUDIES ON A NEW ANTIBIOTIC—BRL.1241

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THE discovery and isolation of 6-aminopenicillanic acid (Batchelor et al. 1959) has made it possible to synthesise a wide range of penicillins with modified properties. One of these, BRL.1241,* has proved highly effective against penicillin-resistant staphylococci.

Methods and Results

In the following experiments BRL.1241 and penicillin G were administered as their sodium salts.

General Pharmacology

In mice and cats no toxic symptoms were observed with single doses of 2.5 g. per kg. intravenously, and in mice and rats with doses of 4 g. per kg. subcutaneously. When BRL.1241 was administered daily to rats for twelve weeks at doses of 100 and 500 mg. per kg. subcutaneously, and to dogs for four weeks at 250 mg. per kg. twice daily subcutaneously, no biochemical, hæmatological, or histological abnormalities were noted. Apart from the discomfort of the injection, the compound was well tolerated. 1% and 10% solutions were injected intramuscularly and intradermally into rats, guineapigs, and rabbits without any local irritation. Similarly, a 1% solution applied daily to the eyes of rabbits was without effect. Administration to anæsthetised cats at a dose of 500 mg. per kg. had no effect on blood-pressure and respiration.

Blood-levels in rabbits and dogs after intramuscular injection resembled those following injection of penicillin G. The mechanism of excretion in chicks was also similar to that of penicillin G. Like penicillin G, BRL.1241 penetrates the blood-brain barrier only with difficulty. It is protein-bound to a lesser degree than penicillin G.

Protection Tests

The protective effect of BRL.1241 was determined in mice infected with *Klebsiella pneumoniæ*, *Salmonella typhimurium*, *Diplococcus pneumoniæ*, *Staphylococcus pyogenes* Smith and *Staph. pyogenes* 52-75, the last organism being highly resistant to penicillin G (minimal inhibitory concentration 125 μg. per ml.).

Of the first four organisms, serial dilutions of 18-24-hour cultures were prepared in 5% hog gastric mucin to enhance the virulence, and 0·5 ml. volumes were injected intraperitoneally. Deaths were recorded over four days and the number of organisms killing 50% of the mice was estimated ($L.D._{50}$). The mice under test were injected with a hundred times this number of organisms.

Penicillin G and BRL.1241 were administered subcutaneously to groups of 10 mice in graded doses to the log base 4, in 0·2 ml. saline immediately following the infection. The mice were observed for four days and the deaths were recorded daily. The percentage deaths were plotted against log dose, and the dose of compound (mg. per kg.) giving protection to 50% of the mice ($C.D._{50}$) was read off from the graph. The estimate of the $C.D._{50}$ against *Staph. pyogenes* 52–75 was carried out in exactly the same way, except that 0·5 ml. of a 1/2 dilution in 5% hog gastric mucin of an overnight culture was used to infect the animals.

The results obtained are given in the table.

* 'Celbenin' is the registered trade name of Beecham Research Laboratories Ltd. for BRL.1241.

A further estimate of the in-vivo effect against penicillin-resistant organisms was carried out using the method described by Selbie and O'Grady (1954). Groups of 10 mice (18–22 g.) were infected by injecting into the muscle sheath of the thigh 0.2 ml. of a 1/2 dilution of an overnight growth of *Staph. pyogenes* Russell (type 80). BRL.1241 in doses of 50, 100, and 200 mg. per kg. and penicillin G 200 mg. per kg. were administered subcutaneously daily for three days, the first injection being given immediately following the infection. An infected control group received no treatment. The maximum thigh diameter of each mouse was measured with callipers on the first, third, and eighth day after the infection. The results (fig. 1) clearly demonstrate a graded response to dose. The activity against other resistant staphylococci has been confirmed.

$C.D._{50}$ VALUES FOR BRL.1241 AND PENICILLIN G DETERMINED IN MICE (10 PER DOSE LEVEL)

Organism	$C.D._{50}$ (mg. per kg.)	
	BRL.1241	Penicillin G
Klebsiella pneumoniæ	Inactive	Inactive
Salmonella typhimurium	Inactive	Inactive
Diplococcus pneumoniæ	10·0	1·0
Staphylococcus pyogenes Smith	1·3	0·2
Staph. pyogenes 52–75 (penicillin-resistant) ..	100·0	Inactive

The activity of BRL.1241 was further confirmed by a subsequent series of experiments, using the technique of Selbie and O'Grady (1954), in which groups of 10 mice were infected with two strains of staphylococci. *Staph. pyogenes* Russell (resistant to penicillin G) was injected into the muscle sheath of the right hind leg, and *Staph. pyogenes* 2187 (sensitive to penicillin G) was injected into the left hind leg. Because untreated mice usually died from this double infection, two control groups were used, one receiving the sensitive strain in the left leg, and the other receiving the resistant strain in the right leg. The

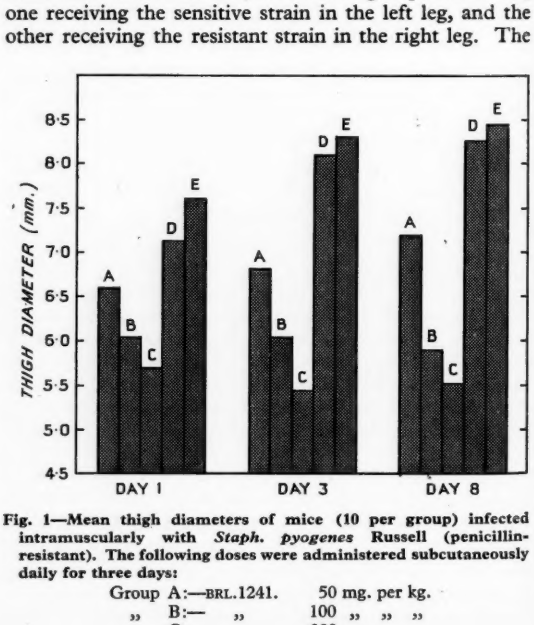

Fig. 1—Mean thigh diameters of mice (10 per group) infected intramuscularly with *Staph. pyogenes* Russell (penicillin-resistant). The following doses were administered subcutaneously daily for three days:

Group A:—BRL.1241. 50 mg. per kg.
„ B:— „ 100 „ „ „
„ C:— „ 200 „ „ „
„ D:—Penicillin G. 200 „ „ „
„ E:—Untreated infected control.

thigh diameters were measured as described above. Penicillin G and BRL.1241 were administered subcutaneously at a dose of 100 mg. per kg. daily for three days. The results (fig. 2) show the effectiveness of BRL.1241 in mice infected simultaneously with both resistant and sensitive staphylococci. Penicillin G is completely inactive against the resistant strain, but more effective than BRL.1241 against the sensitive strain.

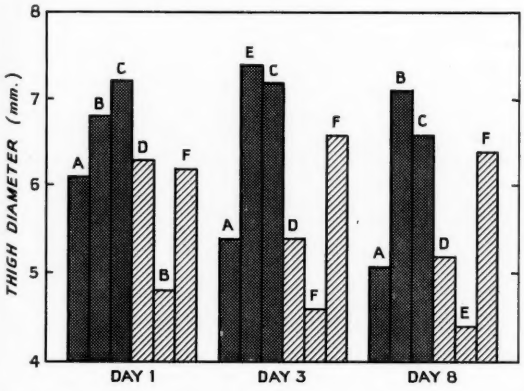

Fig. 2—Mean thigh diameters of mice (10 per group) infected intramuscularly with *Staph. pyogenes* Russell (penicillin-resistant) in the right hind limb and *Staph. pyogenes* 2187 (penicillin-sensitive) in the left hind limb.

BRL.1241 and penicillin G, 100 mg. per kg., were administered subcutaneously daily for three days.

Blocks A, B, and C are the mean thigh diameters of the limb infected with the resistant staphylococcus, and D, E, and F are the mean diameters of the limb infected with the sensitive staphylococcus. Group 1 (A and D) received BRL.1241, group 2 (B and E) received penicillin G, and group 3 (C and F) was the untreated infected control.

Conclusion

BRL.1241 is remarkably free from toxic actions. It can be given in high doses intramuscularly or intravenously. The blood-levels obtained after an intramuscular injection in rabbits and dogs follow a pattern very similar to that obtained after penicillin G. Like penicillin G, it requires large doses before it will penetrate into the cerebrospinal fluid.

BRL.1241 does not combine with serum protein to the same degree as penicillin G. This, however, does not seem to have influenced the cross-allergenic response in patients already sensitive to penicillin (Stewart et al. 1960).

It is highly effective against staphylococci resistant to penicillin G, and the results obtained clearly demonstrate the activity in vivo. Though BRL.1241 is not as effective as penicillin G against sensitive strains of staphylococci, its activity is still considerable. In mice infected with both penicillin-sensitive and penicillin-resistant strains of staphylococci, it was equally active against the two organisms, whereas penicillin G was active only against the sensitive strain. This is in agreement with the in-vitro findings of Knox (1960), Rolinson et al. (1960), Stewart et al. (1960) and Thompson et al. (1960).

We wish to thank Prof. C. A. Keele for his general interest and helpful discussions; Dr. A. A. G. Lewis, physician to the Connaught Hospital, Walthamstow, under whose skilled guidance the dog studies were conducted; and Mr. F. P. Doyle and his colleagues for the preparation of the compound. In addition, we wish to acknowledge the excellent technical assistance of Mr. D. Wright and Mr. M. J. Wilson.

References at foot of next column

A NEW TECHNIQUE FOR THE CONTROL OF HOSPITAL CROSS-INFECTION

EXPERIENCE WITH BRL.1241 IN A MATERNITY UNIT

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THE problem of cross-infection with staphylococci in hospitals is still largely unsolved. While the treatment of cases is an important aspect, the fundamental requirement is to interfere effectively with the epidemiological cycle. Rigorous aseptic surgical technique can keep wound infection to a low level but does not eradicate it. Moreover it cannot be applied to the prevention of such forms of cross-infection as staphylococcal bronchopneumonia in elderly and debilitated patients. Other things being equal, the greater the pollution of the environment by staphylococci, the more readily will wounds and weakened epithelial surfaces become infected. High nasal-carriage rates in normal people, combined with the confined conditions in a hospital, lead to a build-up of staphylococci in the surroundings: the noses of fresh individuals then become colonised in their turn and void more staphylococci into the air and dust. This is the fundamental cycle, the patient being but an accident within it; but once sepsis has become established it also contributes staphylococci to the pool. The introduction of antibiotics has not abolished this cycle, but has tended to eliminate drug-sensitive organisms. Thus the environmental pool of infection has come to consist increasingly of staphylococci resistant to various antibiotics.

It is our belief that the crux of the problem lies in nasal carriage. An observation made by Gould in 1958 suggested that the atmosphere of hospitals contains appreciable amounts of penicillin demonstrable by air sampling, and he concluded that this accounted for the exclusion of penicillin-sensitive staphylococci from the noses of hospital personnel. Since the nose appears to be the main site of multiplication, we decided to make use of this observation in our attempt to break the epidemic cycle. Whereas penicillin excludes only staphylococci which are sensitive to it, leaving others free to multiply, the deliberate introduction into the atmosphere of an antibiotic active against *all* strains of pyogenic staphylococci should completely abolish the nasal carriage of this organism. The spraying of a concentrated solution of such a drug should produce droplet nuclei of the antibiotic, which would follow essentially the same pathways as the staphylococci in the environment. If an adequate concentration could be achieved on the nasal mucosa, the main source of staphylococci would be cut off, and the concentration of staphylococci in the surroundings would gradually diminish. This in turn should lead to a reduction in cross-infection.

MR. BROWN, MR. ACRED: REFERENCES

Batchelor, F. R., Doyle, F. P., Naylor, J. H., Rolinson, G. N. (1959) *Nature, Lond.* **183**, 257.
Knox, R. (1960) *Brit. med. J.* ii, 690.
Rolinson, G. N., Stevens, S., Batchelor, F. R., Cameron Wood, J., Chain, E. B. (1960) *Lancet*, ii, 564.
Selbie, F. R., O'Grady, F. (1954) *Brit. J. exp. Path.* **35**, 556.
Stewart, G. T., Nixon, H. H., Coles, H. M. T., (1960) *Brit. med. J.* ii, 703.
Thompson, R. E. M., Harding, J. W., Simon, R. D. *ibid.* p. 708.

The drug of choice for this purpose should be highly active against *all* pyogenic staphylococci. Its continued use should not lead to the emergence of resistant strains. It must not be irritating or cause hypersensitivity phenomena.

BRL.1241* is a synthetic derivative of 6–aminopenicillanic acid which retains the biological activity of penicillin but is invulnerable to staphylococcal penicillinase (Rolinson et al. 1960). Its properties were studied by us to assess its suitability for the kind of use envisaged. To test our general hypothesis we selected a maternity unit for aerial spraying, since infants are born bacteriologically sterile and regularly acquire *Staphylococcus pyogenes* in the nose by inhalation.

Experiments

PROPERTIES OF BRL.1241

Bacteriostatic effect.—We have confirmed the statement of Rolinson et al. (1960) that strains of *Staph. pyogenes* are sensitive to concentrations of 1·5 to 3 μg. per ml. 400 strains from routine isolations were tested, and without exception they were all sensitive to this dose. The material consisted largely of strains resistant to various other antibiotics, as shown in fig. 1. It is noteworthy, however, that a number of coagulase-negative micrococci were encountered which were resistant to this concentration.

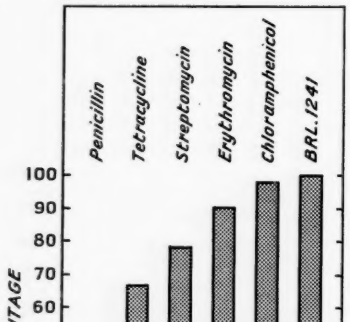

Fig. 1—Sensitivities of 400 strains of staphylococci isolated from inpatients and outpatients.

Bactericidal effect.—The antibiotic is, moreover, highly bactericidal at a concentration of 6 μg. per ml. (fig. 2). A 99·9% reduction of the viable count of a large inoculum (10^8) was achieved within ten hours. Lysis of the organisms occurred in the presence of 5 μg. per ml. in broth cultures, as indicated by optical density measurements.

Emergence of resistant strains.—As naturally occurring resistant strains were not found, attempts were made to encourage the emergence of resistant mutants. 12 strains of various phage groups showing multiple resistance to other antibiotics were subjected to 20 serial passages on gradient plates (Szybalski and Bryson 1952) containing BRL.1241. This method is known to reveal resistant mutants readily, but no mutants resistant to BRL.1241 were found. All 12 strains showed approximately the same sensitivity in broth cultures after the 20 passages as they had shown before. In some instances there were colonies on areas of gradient plates containing an apparently high concentration of the drug, but when these were subcultured on nutrient agar and tested they showed their original sensitivity.

Other properties.—The drug is a white crystalline odourless powder, readily soluble in water. A solution containing 1000 μg. per ml. lost all activity in two days at 37°C in five days at 22°C, and in eight days at 10°C. Solutions kept frozen were stable for several weeks. The dry powder is stable at ordinary room temperature. For our purposes it was more convenient to keep solutions frozen than to dispense the powder each time.

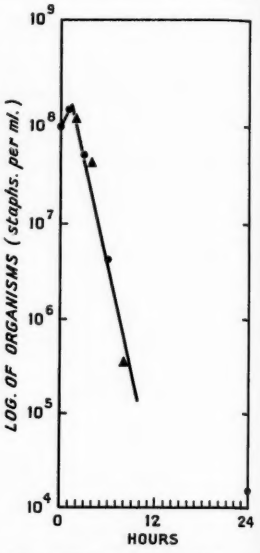

Fig. 2—Effect of BRL.1241 on the viable count of two strains of *Staph. pyogenes* (6 microgrammes per ml.).

EFFECT ON STAPHYLOCOCCAL CARRIAGE

Nasal Carriage in Unit Before Treatment

The maternity unit contained two practically identical sections, ward A and ward B. Each consisted of a ward and nursery and they were separate physically, but shared their nursing staff. Normally the babies were nursed with their mothers. Ward A together with its nursery occupied approximately 15,000 c. ft.

As a preliminary investigation, nasal swabs were taken daily from 29 babies born consecutively in ward A until *Staph. pyogenes* was isolated. It was assumed that they remained carriers for the rest of their stay in hospital (fig. 3A). To test this point, 29 consecutive infants were similarly swabbed every day for 10 days in ward B. The results in fig. 3B show that the assumption is broadly correct. It can be seen that the staphylococcal nasal carriage of the infants in both wards was over 50% of all the swabs taken. This is in agreement with the findings of others (Cunliffe 1949). All but 1 of the strains of staphylococci isolated from these babies were resistant to penicillin, and about half were also resistant to other antibiotics.

EFFECTS OF SPRAYING

Effect on nasal carriage.—The first experiment consisted of spraying in ward A 1·0 gramme of the drug dissolved in 20 ml. of distilled water from a universal container fitted with a 'Spraydex' plastic window-cleaning spray unit. The fluid was sprayed as evenly as possible over all parts of the ward and nursery (fig. 4). This took about two minutes. Spraying was done once a day and nasal swabs were taken daily as before. The results are shown in fig. 3C. There was a reduction in the number of positive isolations from 50 to 24%. There was also a very marked reduction in the number of colonies grown from positive swabs.

Spraying 1·0 g. four times a day was next tried, after a short break, on another series of 29 babies. The results are shown in fig. 3D. Though there was a further reduction in the isolations of *Staph. pyogenes* to 12·4% of all swabs, it was noticed that all the isolations occurred during the first six weeks of this experiment, suggesting a cumulative effect. Hence the experiment was continued for a further 29 babies without a break. The results (fig. 3E) revealed only 6 positive isolations out of 290 nasal swabs, and some of these were only single colonies. The noses of most of the babies had become colonised, however, by coagulase-negative micrococci. Many of these were resistant to BRL.1241. Some colonisation by gram-negative flora was also observed.

Effect on umbilical and rectal carriage.—This was not studied

* This drug is marketed by Beecham Research Laboratories Ltd. under the registered trade name 'Celbenin'. It was previously referred to by us as AB.1241 (Elek and Fleming 1960).

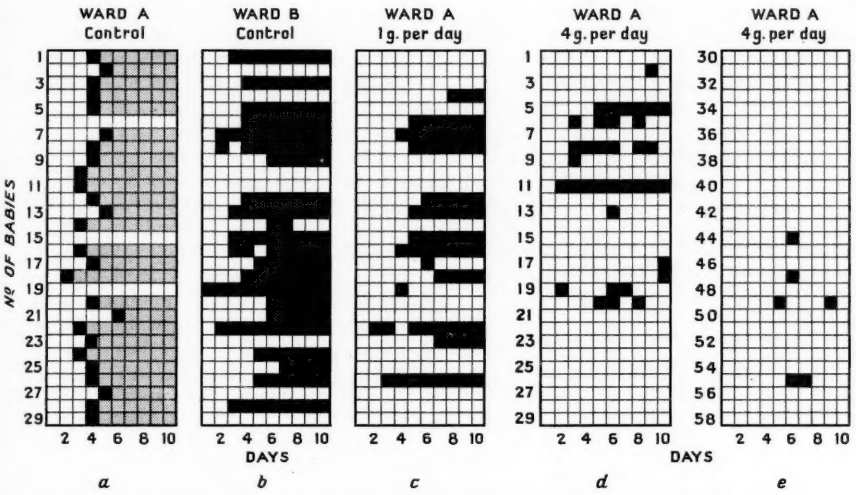

Fig. 3—Nasal carriage of *Staph. pyogenes* by newborn infants showing the effect of spraying BRL.1241.
Each figure represents the results of daily swabbing of a series of 29 babies.
Each horizontal column represents one baby and each square represents one day.
The days on which staphylococci were isolated are indicated in black.
The stippled area in fig. 3A indicates days in which nasal carriage is presumed.

systematically, but swabs were taken from the rectal and umbilical areas of a number of babies on the tenth day. Of 29 babies swabbed in ward A only 2 isolations were made from rectal swabs, while the control ward B gave 14 positives out of 25. Of 29 umbilical swabs in ward A, 6 were positive, while in the control ward there were 11 positives out of 26.

Effect on occurrence of staphylococcal lesions.—During six months of spraying 4·0 g. a day a total of 340 babies were born in the unit, approximately equally divided between wards A and B. Altogether there were 14 minor lesions, mostly sticky eyes and pimples from which *Staph. pyogenes* was isolated. None of these were isolated from the babies exposed to the drug by spraying, although the babies in both wards were looked after by the same nurses.

Nasal carriage in mothers and nurses.—58 nasal swabs were taken from the mothers on the first day in ward A, but not necessarily before they were exposed to the drug. Of these, 11 yielded *Staph. pyogenes* of whom, after five days' exposure, only 1 still gave a positive isolation. Nasal swabs from nurses on the unit failed to reveal the carriage of staphylococci resistant to BRL.1241.

Fig. 4—The spray in use.

Hypersensitivity to the drug.—No hypersensitivity phenomena were observed in the babies, mothers, or nurses.

Examination of dust.—(A) After six months' spraying the dust in ward A was found to have an inhibitory activity corresponding to 200 μg. of BRL.1241 per g. (B) The number of staphylococci in the dust of both wards was estimated by culturing serial dilutions of dust suspensions in salt meat broth (Maitland and Martyn 1948). By this method approximately 20,000 pyogenic staphylococci per g. were found in ward B, whereas none were demonstrated in the dust from ward A.

Air Sampling

Samples of air were taken after spraying 1·0 g. of BRL.1241 into ward A. 15 c. ft. of air sampled in the first fifteen minutes by means of a Bourdillon slit sampler was found to contain about 50 μg. of the antibiotic. Over the next two hours, however, similar samples showed only small amounts, in the form of occasional particles containing a few microgrammes each.

Discussion

BRL.1241 seems to meet all the requirements for a drug to be used for spraying. It is highly bacteriostatic and bactericidal to *Staph. pyogenes*, and, as it is stable in the dry form, the droplet nuclei probably retain activity. Six months' continuous spraying resulted in no untoward side-effects such as irritation of mucous membranes or hypersensitivity. No strains of pyogenic staphylococci naturally resistant to it were encountered, nor did resistant strains appear during the period of spraying.

The most important theoretical objection to this use of the antibiotic is the possibility of selecting drug-resistant mutants, thereby eventually interfering with its therapeutic use. The attempt to obtain resistant mutants on " gradient plates " (described above) constitutes a stringent test, and failure to obtain resistant strains in this way is of evidential value. Though we cannot say that the emergence of BRL.1241-resistant staphylococci is impossible, we think it highly unlikely. The new drug is based on the active portion of penicillin, and resistance to it would be expected to develop by mechanisms similar to those operating in regard to penicillin. These are of two kinds, of which only one is clinically important. In clinical lesions, the resistance of staphylococci to penicillin is entirely due to formation of penicillinase. The prevalence of such penicillinase-producers is almost certainly due to the selection of strains already extant when penicillin was introduced for treatment. Increase by selection in this manner is improbable, since no BRL.1241-resistant strains were met either in our own or other large series investigated (Thompson et al. 1960, Stewart et al. 1960). The acquisition of penicillinase activity in vitro by a strain is difficult to demonstrate, and if it occurs at all in vivo must be exceedingly rare. BRL.1241 is resistant to staphylococcal penicillinase, and, since the new drug has a molecular configuration which probably does not occur naturally, the acquisition of an enzyme directed against it by a single mutational step, or even by a few steps, is accordingly remote.

The other mechanism of penicillin resistance is of no clinical importance whatsoever. It occurs when a strain is artificially maintained in vitro in concentrations of the

drug higher than those to which it was initially sensitive. Such strains lack penicillinase, are never isolated from lesions, and are deprived of virulence. Variants of this kind, tolerant to BRL.1241, if they occurred at all, would similarly be expected to be devoid of virulence and so could not become established as human pathogens.

The idea of dealing with the nasal reservoir is not novel. The application of an antibiotic or antiseptic ointment to the nose, however, has both practical and theoretical disadvantages. Being laborious and æsthetically objectionable, it is often neglected. More important is the fact that it may not reach the "business area" where staphylococci thrive. After spraying, the droplet nuclei circulate in air and dust in the same way as staphylococci and reach the same places. Thus with only a few minutes' spraying daily it is possible to achieve a circulation of the drug which reaches the breeding ground of staphylococci. Furthermore, this method includes everyone in the environment.

The results of spraying in the maternity unit leave no room for doubt that the colonisation of babies' noses can be prevented by this means. It is well known that infants usually leave hospital carrying the prevalent "hospital staphylococcus" which shows multiple antibiotic resistance. Such organisms may then cause breast abscesses in the mother and other infections in the home. The prevention of this alone would justify the new technique. Of wider import, however, is the fact that it proves the hypothesis that the epidemic cycle can be broken in this manner.

A progressive effect was shown: at first there was only a reduction in nasal carriage, but in the later stages there were practically no *Staph. pyogenes* to be found. This apparently cumulative effect of spraying may be due to three factors:

1. There may be a continuous build-up of active BRL.1241 particles in the environment since the drug is stable in the dry form.

2. There is a progressive reduction in nasal excretion of staphylococci by the infants, shown by a fall in the number of positive swabs and also by the growth of fewer colonies from those which were positive. This necessarily leads to a decrease in the supply of staphylococci and therefore to the reversal of the vicious cycle. It is noteworthy that the time-honoured stratagem of closing a ward in the face of widespread sepsis operates in exactly the same way.

3. The elimination of coagulase-positive staphylococci by BRL.1241 allows the establishment of other more resistant micrococci in the nose. This flora may conceivably play a part in keeping out *Staph. pyogenes* by antibiosis. If this were so, the colonisation of noses with a population of resistant non-pathogenic micrococci may be a definite advantage.

Which of these factors is most important cannot yet be said.

We do not wish to suggest that the method of spraying employed, though a simple one, is the most economical or the best adapted for the purpose. Variation in the amount of the drug, in relation to space, frequency of spraying, and the correct degree of nebulisation, awaits further study. It may be that the dissemination of the drug as a fine powder will be best.

We believe that staphylococcal cross-infection in hospitals can be best countered by breaking the epidemic cycle at its most vital point—the nasal reservoir—and removing the infective source by isolation and treatment of cases. Our findings make it clear that prevention of colonisation of infants by *Staph. pyogenes* is possible. The ultimate aim is to abolish existing colonisation in the noses of adults. Our limited observations on the mothers suggest that this, too, is possible. The problem needs further study as to dosage and conditions of administration. In presenting these findings, our aim is to stimulate such research.

Summary

Staphylococcal cross-infection in hospitals is the result of a cycle in which the major source of the organisms is the nasal reservoir of the personnel and patients. From this site of multiplication, staphylococci are voided into the air and dust, whence they colonise fresh noses. Clinical sepsis is but an accident within the cycle.

Spraying BRL.1241 into the air by a simple method was shown to prevent the usual acquisition of pyogenic staphylococci by newborn infants.

Spraying produces droplet nuclei of the drug, which circulate in the air in the same way as staphylococci. Thus it is possible to break the cycle by physiological means at its focal point—the nasal reservoir. The properties of BRL.1241 seem to render it the ideal drug for this purpose.

The new method is economical in labour and materials and is recommended as a basis for further research into the prevention of staphylococcal cross-infection.

We should like to thank the medical and nursing staff of the maternity department at St. George's Hospital for their kind cooperation in this work. Our thanks are also due to the Beecham Research Laboratories for letting us have a supply of the drug for this trial.

REFERENCES

Cunliffe, A. C. (1949) *Lancet*, ii, 411.
Elek, S. D., Fleming, P. C. (1960) *ibid.* i, 1009.
Gould, J. C. (1958) *ibid.* i, 489.
Maitland, H. B., Martyn, G. (1948) *J. Path. Bact.* **60**, 553.
Rolinson, G. N., Stevens, S., Batchelor, F. R., Cameron Wood, J., Chain, E. B. (1960) *Lancet*, ii, 564.
Stewart, G. T., Nixon, H. H., Coles, H. M. T. (1960) *Brit. med. J.* ii, 703.
Szybalski, W., Bryson, V. (1952) *J. Bact.* **64**, 489.
Thompson, R. E. M., Harding, J. W., Simon, R. D. (1960) *Brit. med. J.* ii, 710.

RENAL TRANSPLANTATION BETWEEN IDENTICAL TWINS

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THE first successful renal transplantation between identical twins was performed in 1954 by Merrill et al. (1956) at the Peter Bent Brigham Hospital, and since that time a total of eight such operations have been reported by the same group (Murray et al. 1958). The present report is concerned with another such transplantation performed at the Royal Victoria Hospital, Montreal, in May, 1958, and includes details of the immediate preoperative period and the first postoperative year. The recipient twin was managed on a metabolic-balance regimen in the early postoperative period and some of the studies of this period will be published separately (Dossetor et al. 1960).

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Case-report

PREOPERATIVE PERIOD

The patient was a 15-year-old white girl who was admitted on March 31, 1958, as an emergency to the Montreal Neurological Institute because of the sudden onset of epileptiform seizures associated with hypertension. She had been in apparent health until the morning of admission. She had noticed some heaviness of the head on wakening that morning, and the first seizure occurred several hours later. Further seizures precipitated status epilepticus. Inquiry into her previous health revealed that at the age of 4 years she had had an urinary infection which had been treated for several days with penicillin and which had given no further symptoms. During the months prior to admission there had been no headache, no shortness of breath on exertion, no dysuria, and no polyuria or nocturia. She had been admitted to a hospital three years previously for tonsillectomy, and examination of the urine at that time was reported as normal.

On examination at the time of admission she was unconscious from the effects of the seizures as well as intravenous barbiturate. The abnormal findings were bilateral papilledœma and hypertension of 185/140 mm. Hg. There was no evidence of localised neurological disease. The fact that her hypertension might be secondary to renal disease was suggested by a " three-plus " proteinuria, and the urinary sediment contained one to two white blood-cells per high-power field and a number of hyaline casts containing granules, as well as rare mixed epithelial and white-blood-cell casts. She was immediately given 2·5 mg. reserpine intramuscularly to control the blood-pressure. The serum level of non-protein nitrogen at this time was 82 mg. per 100 ml.

The patient was fully conscious within 36 hours and her blood pressure had been controlled. There were no residual neurological signs. The urine on culture had grown pseudomonas organisms, and bilateral pyelonephritis with hypertension was diagnosed. As she had an identical twin sister steps were taken to explore the possibility of a renal-transplant operation should the return of renal function, after treatment of the urinary infection, not be adequate. These steps were as follows: (*a*) to investigate further the patient's disease; (*b*) to establish that the potential donor twin had a normal urinary tract; (*c*) to obtain as much proof as possible that the two twins were genetically identical; (*d*) to obtain legal authorisation for the operation; and (*e*) to control the management of the potential recipient during the preoperative period.

Investigation of Recipient Twin

Within 3 days of the start of antibiotic therapy for the urinary infection the urine became sterile, and it remained sterile thereafter. However, as fig. 1 shows, the serum-non-protein-nitrogen rose to 175 mg per 100 ml. during the 1st week and, even after control of the infection, the level did not fall below 60 mg. per 100 ml. The hæmoglobin on admission was 86%; the white blood-cell count was 11,200 per c.mm.; the electrocardiogram was suggestive of left ventricular hypertrophy; chest X-ray showed normal cardiac contour, clear lung fields; serum electrophoretic pattern showed slightly lowered albumin; plain X-ray of abdomen showed small kidneys, and a retrograde pyelogram showed no obstructive element. Cystoscopic examination revealed a normal lower urinary tract. Endogenous-creatinine clearance measured on two 24-hour samples gave the figures of 5 ml. per minute on each occasion, and open renal biopsy showed chronic pyelonephritis to be present.

Examination of Donor Twin

The urinalysis of the donor twin was normal, and her endogenous-creatinine clearance was 102 ml. per minute. Intravenous pyelography was normal; hæmoglobin was 90%; and on physical examination no abnormality was found.

The Proof of Identity

This was undertaken by Dr. F. Clarke Fraser and Dr. J. D. Metrakos, of the Department of Genetics, McGill University. The examination showed that, as well as appearing to be identical, the twins had similar dermatoglyphic patterns on all fingers and toes and the ridge counts were similar. Comparison of blood-groups showed them to be identical, these results being confirmed by Dr. Levine of the Ortho Laboratories, Raritan, New Jersey. The conclusion was that the twins were monozygotic. Skin-grafting was performed between the two twins by Dr. M A. Entin, and both grafts took successfully. The graft on to the donor twin was biopsied four weeks later and no evidence of necrosis was found.

Authorisation for Operation

An operation on a healthy person representing a " mutilation " procedure is not covered by existing legislation, and special permission had to be obtained. This consisted of a family council convened before a lawyer with affidavits from the surgeon and the donor twin. A petition was then submitted to the Associate Chief Justice of the Province of Quebec who confirmed the family council's resolution.

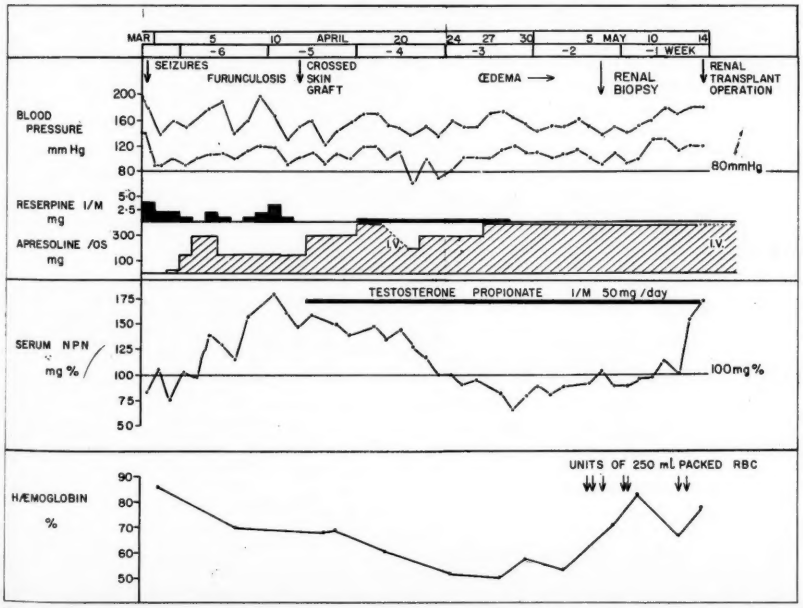

Fig. 1—Record of preoperative blood-pressure and its control; of degree of uræmia and period of testosterone therapy; and of hæmoglobin level.

Preoperative Management of Recipient Twin

The preoperative $6^1/_2$-week period is outlined in fig. 1. The blood-pressure was brought under control initially with intramuscular reserpine, and thereafter a combination of intramuscular reserpine and oral hydrallazine was used. At times the patient could not take oral preparations and the hydrallazine was given intravenously. It can be seen that despite these measures the blood-pressure was not brought down to normal levels and the diastolic

pressure remained at approximately 100 mm. Hg during most of the preoperative period. Despite the control of the urinary infection within 3 days, the serum level of non-protein nitrogen rose in the 1st week and thereafter fell slowly. At the peak of the rise in serum-non-protein-nitrogen testosterone propionate 50 mg. daily intramuscularly was begun, to retard the rate of endogenous protein catabolism (Kenyon et al. 1940, Masson et al. 1949). In addition to this, the protein intake was progressively reduced. There was no protein in the diet in the few days before the operation. However, it can be seen that the non-protein-nitrogen level of just under 100 mg. per 100 ml. was not maintained during the last 2 preoperative days when a rapid rise occurred for reasons that are not clear. The patient's hæmoglobin was 85% on admission, but she became more anæmic and had to be transfused with a total of 7 units of 250 ml. of packed red cells in the 10 days before the transplantation operation.

During the early preoperative weeks it seemed that electrolyte balance could be achieved without a specifically controlled diet, though moderate sodium restriction was enforced. For this reason all dietary restriction of electrolyte intake was removed in the 4th preoperative week. The patient selected a diet that was high in sodium and chloride, and by the middle to the 3rd preoperative week she had become œdematous in the thighs, lumbosacral region, and periorbitally. There was a 7 lb. rise in weight to 99 lb. The urinary excretion of sodium was found to have fallen to very low levels (less than 5 mEq. per day) so the patient was placed on a rigid salt restriction.

The reason for the low sodium output did not seem to be a reduced filtered load of sodium as the blood-pressure was not significantly lower during this time, nor was there a rise in the values of serum-non-protein-nitrogen. In fact, as can be seen in fig. 1, the serum-non-protein-nitrogen level fell during the first 2 weeks of testosterone therapy; the decrease was due, in all probability, to the anticatabolic effect of the hormone besides, to a lesser degree, the dilutional effect of the excess extracellular fluid.

It seems that testosterone also caused the sodium retention. Kenyon et al. (1940) demonstrated that testosterone could have this effect, and probably this tendency would be more pronounced in a subject who had a reduced filtration-rate due to renal disease. Freedman and Spencer (1957), however, noticed no weight gain in ten uræmic subjects treated with testosterone, but sodium balance was not done.

As the increased tendency to retain sodium seemed to be due to an increase in the tubular reabsorption it could, perhaps, be counteracted by a diuretic. An organic mercurial diuretic was used. Any further damage to the diseased kidney would not be important as the transplanted kidney would take over within a short time. Natriuresis was caused by each mercurial injection. With these injections and strict control of sodium intake (10 mEq. per day), the œdema went and the weight was reduced to 93 lb. by the time of operation.

During the few days before the operation the patient was vomiting and was stuporose. The blood-pressure became difficult to control and her condition was critical on the day of operation. Dialysis was considered but was not performed as it was felt that she would tolerate surgery.

OPERATION OF TRANSPLANTATION

This was done by two surgical teams in adjacent operating-rooms. In one room the urological surgeon, Dr. K. J. MacKinnon, exposed the left kidney of the donor twin by an incision below the twelfth rib and prepared the vessels for ligation at the appropriate moment. The left ureter was mobilised as far as the pelvic brim. While this was being done Dr. J. C. Luke prepared the anastomotic site. The abdominal wall was opened through a Gibson incision which was extended at its lower extremity across the midline above the symphysis pubis. The peritoneum of the right iliac fossa was reflected upwards and medially. The common iliac artery was identified, and the internal and external iliac arteries were dissected from surrounding tissues. When it was established that there was only one renal artery supplying the donor kidney, the recipient's internal iliac artery was clamped and severed and its branches were ligated and divided. The external iliac artery was freed to the inguinal ligament. It was found that rotation of the internal iliac artery posterior to the external iliac artery produced less angulation than anterior (lateral) rotation.

The vessels were ligated close to the aorta and inferior vena cava, the ureter was divided, and the kidney was removed. The kidney was not perfused; it was taken directly to the adjacent operating-room and placed in the right iliac fossa of the recipient, and the vascular anastomosis was performed. There were two renal veins draining the donor kidney. These two veins were first anastomosed, end-to-side, to the common iliac vein and external iliac vein and then the artery was anastomosed, end-to-end, to the internal iliac artery. When the tapes and clamps were removed the kidney showed an immediate and apparently complete vascularisation. The period of total ischæmia of the kidney was 58 minutes.

The ureterovesical anastomosis was then performed. The bladder wall was opened through a vertical incision 1 in. to the right of the midline and a point chosen for ureteral anastomosis $1^1/_2$ in. above and slightly lateral to the right ureteral orifice. A muscular tunnel was fashioned through the right lower wall of the bladder beginning 2 in. above the site chosen for anastomosis. While this was being done there was visible peristalsis in the ureter of the donor kidney and already some excretion of urine had occurred. The ureter was threaded through the muscular tunnel and, after removal of $3^1/_2$ in. of redundant donor ureter, the end was anastomosed to the mucosa of the bladder with 4 sutures of atraumatic chromic catgut. When the ureteral anastomosis was completed a rapid osmotic diuresis occurred. Before the bladder was closed a jet of urine, showing some peristaltic fluctuation, was seen to reach up to several inches from the base of the bladder. Extrinsic denervation had not apparently altered the peristalsis of the ureter. A small-calibre polyethylene catheter was passed to the renal pelvis and brought through the cystostomy wound. A no. 24 Foley catheter was placed in the bladder cavity and the bladder closed around both catheters. Drains were inserted in the prevesical space and the iliac fossa and the wound was then closed.

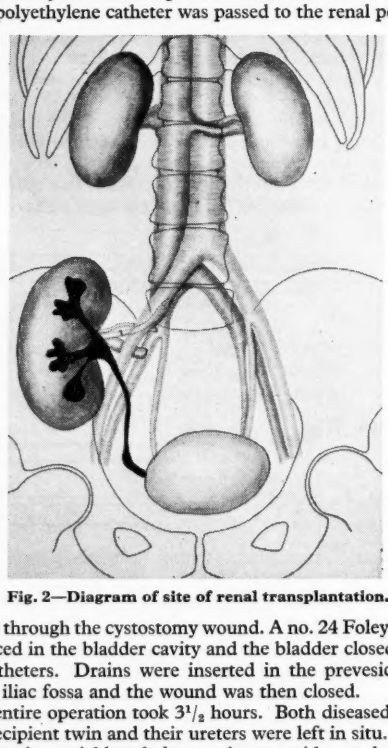

Fig. 2—Diagram of site of renal transplantation.

The entire operation took $3^1/_2$ hours. Both diseased kidneys in the recipient twin and their ureters were left in situ. During the operation trichlorethylene, nitrous-oxide, and epidural anæsthesia were used. The blood-pressure during the operation was stable at about 150/100 mm. Hg.

Fig. 2 illustrates the end results, anatomically, of the operation.

Heparin (750 international units) was given to the recipient

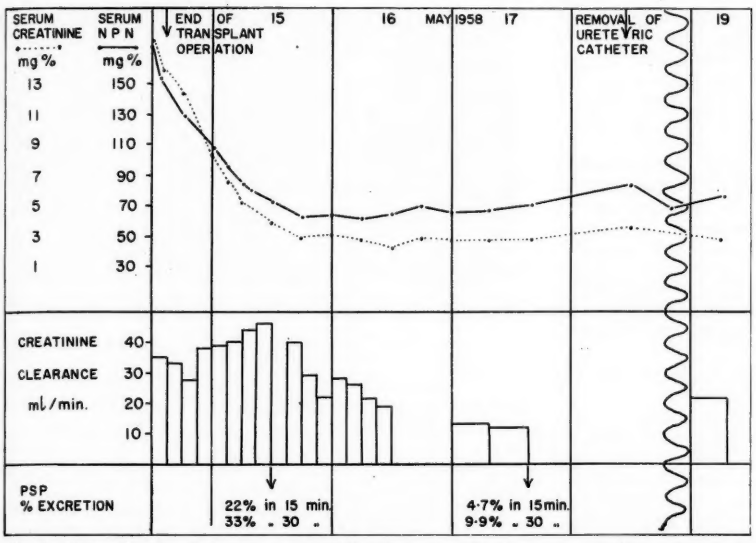

Fig. 3—Rate of fall of serum non-protein nitrogen and of serum creatinine during the first 4½ postoperative days; endogenous-creatinine clearance; and % excretion of phenolsulphonephthalein.

twin approximately one hour before the anastomosis was begun, but no further anticoagulant was given. Towards the end of the operation the recipient twin passed a melæna stool of approximately 300 ml. The donor twin was not heparinized.

THE POSTOPERATIVE PERIOD

A rotation of three special nurses had been previously arranged. The patient's room had had all drapes and blinds removed—the room and all equipment had been thoroughly cleaned with 'Lysol' solution. Strict operating-room technique was used to minimise the risk of infection (Harris and Dossetor 1959).

Gastric drainage was maintained postoperatively, and all calories and electrolytes were administered intravenously through a caval catheter for 6 days. Thereafter the patient took food by mouth and supplemental parenteral therapy was given.

Tetracycline and penicillin were given intravenously—tetracycline 1 g. a day, penicillin 3 million units a day, for the first 2 weeks. Thereafter patient was given sulphamethoxypyridazine 500 mg. a day, for 4 weeks.

The blood-pressure immediately after operation was 120/80 mm. Hg. From the 3rd to the 5th day the blood-pressure gradually rose to 155/100 mm. Hg mean value. The patient was then restarted on reserpine 0·25 mg. three times a day. Within another 5 days the mean blood-pressure was 140/90, and it continued around this range for another 3 weeks. Thereafter reserpine was discontinued, and the mean pressure during the latter part of her stay in hospital was around 120/90 mm. Hg.

At no time from the end of the renal transplant operation was the blood-pressure a cause for anxiety or energetic treatment.

Fig. 3 shows the changes in the level of serum creatinine and non-protein nitrogen during the first 5 days with the changes in endogenous-creatinine clearance and the percentage excretion of phenolsulphonephthalein (P.S.P.). It is evident that the serum levels of creatinine and non-protein nitrogen fell very fast during the first 24–36 hours, but thereafter these levels remained steady and in fact on the 4th day showed a tendency to rise. The presence of the polyethylene catheter might have been a mechanical factor hindering free drainage so this was removed. The glomerular filtration-rate had diminished from May 15 to 17, the decrease being delayed until about 24 hours after the end of operation itself. There was a similar decrease in the percentage of excretion of P.S.P.

A very pronounced osmotic diuresis occurred in the first 9 hours after the end of transplantation, with urine volumes of 800 ml., 500 ml., and 400 ml. in the first three 3-hour periods. With these high flow-rates there was increased loss of sodium and chloride. On the 2nd day, however, the urine volumes were approximately 200 ml. in each 3-hour period at first and then fell to less than 100 ml. in a 3-hour period. This pronounced fall in the 3-hourly urine volume coincided with the levelling off of serum creatinine and non-protein nitrogen. There was no response to a water load of 1000 ml. of 5% glucose and water. The fluid was retained with a 2 lb. gain in weight. An increase in urine volume with a slight increase in sodium and chloride excretion occurred in response to the osmotic effect of 300 ml. of 60% glucose. The plasma-

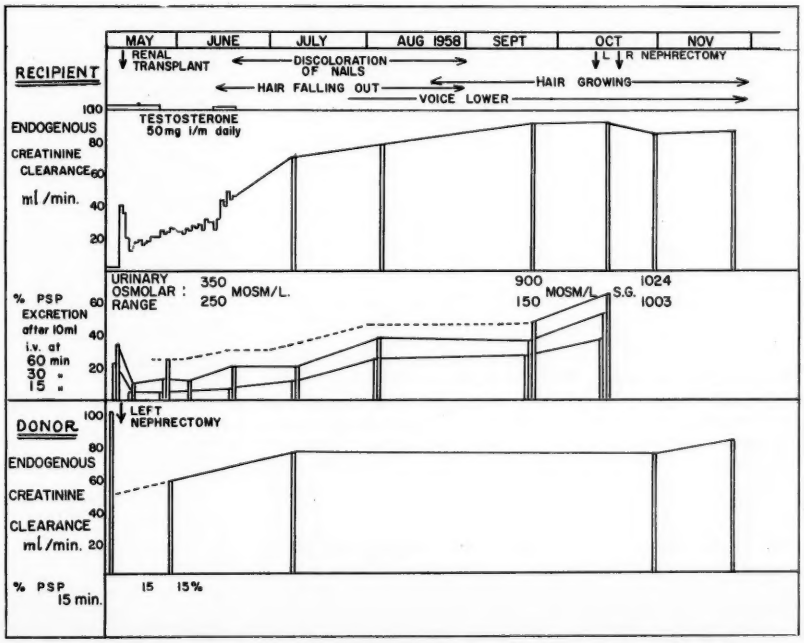

Fig. 4—Renal function tests on both twins during 6 months after renal transplantation.

bicarbonate level rose from 16·9 mEq. per litre at its lowest to about 25 mEq. per litre after the first 2½ days. The rate of excretion of potassium in the phase of osmotic diuresis was not excessive and was only slightly greater than the 3-hourly loss of potassium during the subsequent days. Rapoport et al. (1949) reported that excretion of potassium does not increase in osmotic diuresis.

The patient's condition improved rapidly in the first 3 days after the operation. Within 24 hours her stupor had gone and within 4 days she was alert and felt well. The Foley catheter draining the bladder and the two diseased kidneys provided no urine at all but was irrigated 6-hourly with 1% neomycin solution. The vena caval catheter was removed on the 4th day and the gastric tube was removed the next day. She was hungry and was allowed oral feedings, which were gradually increased in calorie and protein content. The balance of electrolyte intake was given by parenteral infusion.

The catheters were removed on the 4th postoperative day and a Foley catheter was passed to the bladder.

When the cystostomy sinus appeared to be healed the Foley catheter was removed and spontaneous voiding was anticipated. However, only small amounts of bloodstained urine were passed. On the following morning the rectal temperature was 104·2°F and there was considerable pain extending over the whole suprapubic area and up into the right flank. It was thought that this represented either extravasation of urine from the bladder into the extravesical space or vesicoureteral reflux. On reinserting the urethral catheter this discomfort and pain disappeared and the temperature returned to normal. The white-blood-cell count at this time was 30,000 per c.mm. 4 days later the Foley catheter was clamped for 4 hours, and again tenderness developed in the hypogastrium and in the right lower quadrant and the temperature rose. During the 4th postoperative week the catheter was again removed and the patient voided spontaneously without pain. She was awakened every 3 hours at night and made to void to prevent accumulation of urine in the bladder. By this time the patient was eating well and showing a rapid return to normal health; and she was allowed up, the degree of activity being increased each day.

The hæmatological findings were as follows. There was a reticulocyte count of less than 1% during the first 2½ weeks. By the end of the 3rd week the reticulocyte-count was 2·5% and subsequently it was 4%. It remained raised during the remaining weeks in hospital. At the time of discharge the hæmoglobin was 13 g. per 100 ml. (84%).

The donor twin's recovery from simple nephrectomy was quite uneventful.

THE FOLLOW-UP PERIOD

At the time of discharge from hospital the recipient's urine was sterile on culture and the urinary sediment included white blood-cells only, with no casts. She was discharged on oral prophylactic doses of antibiotic and was seen at lengthening intervals during the 6 months between the transplantation and the subsequent bilateral nephrectomy. During this period several changes occurred.

Changes in renal function, both in the 6-week postoperative period in hospital and in the subsequent 6-month follow-up period, are indicated in fig. 4. The creatinine clearance increased gradually from the 3rd postoperative day until the time of discharge from hospital in mid-June. These figures for endogenous-creatinine clearance are based on a single blood measurement of the serum-creatinine level and a total of 24-hour urinary creatinine excretion. The subsequent creatinine clearances were based on two 1-hour clearance periods with blood drawn at the mid-point. It can be seen that the creatinine clearance increased quite rapidly in the first 2 months after the operation and levelled off by the 4th month at a figure of about 90 ml. per minute. Function in the transplanted kidney increased considerably despite the depression of function in the 3 days after transplantation. 4 months after operation the creatinine clearance for the single transplanted kidney was almost the same as that of the two kidneys in the normal donor twin prior to nephrectomy.

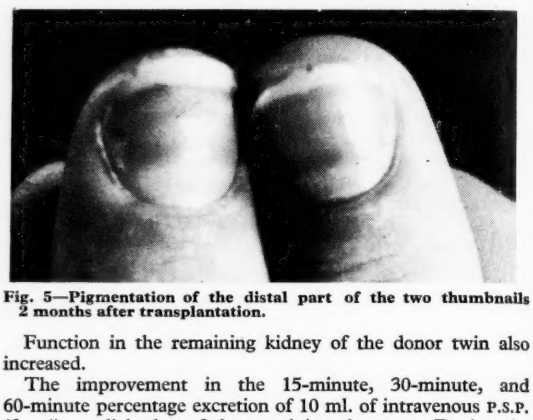

Fig. 5—Pigmentation of the distal part of the two thumbnails 2 months after transplantation.

Function in the remaining kidney of the donor twin also increased.

The improvement in the 15-minute, 30-minute, and 60-minute percentage excretion of 10 ml. of intravenous P.S.P. (fig. 4) parallels that of the creatinine clearance. During the time in hospital the range of osmolality of the urine in the recipient twin was between 250 and 350 mOsm. per litre. 3 months later, the range of osmolality of the urine was from 150 to 900 mOsm. per litre—approximately equivalent to a specific gravity range of 1003 to 1024. In February, 1960, the recipient twin's creatinine clearance was 83 ml. per minute, and the donor twin's was 85 ml. per minute. Both urine sediments were normal and cultures were sterile.

Several other changes in the recipient twin were noticed during this period between the two operations. Shortly after she was discharged from hospital she noticed that her hair was falling out. This began with a bitemporal recession of the hairline and then thinning at the vertex, and subsequently practically all the hair fell out. About the same time it was noticed that her voice was noticeably lower. Although the falling hair could have been due, non-specifically, to the seriousness of her illness the lowering of her voice must have been due to the prolonged testosterone therapy. Menstrual periods did not return for 3 months after the operation, by which time the hair was growing back. However, the voice remains lower than that of her twin sister.

Another feature of interest was that the distal half of her fingernails and toenails was noticeably darker than the more

Fig. 6—Intravenous pyelogram 6 weeks after transplantation.

proximal part; the more proximal part was the normal colour (fig. 5). This pigmentation probably represents the urochrome pigments that are known to be retained within the body in uræmia and which became incorporated into the substance of the nails. The patient was not thought to have been pigmented before operation.

5 months after operation the recipient twin was readmitted for bilateral nephrectomy. This was performed by Dr. K. J. MacKinnon in two operations 1 week apart, and these were uneventful. The blood-pressure which had remained slightly raised after transplantation regressed to normal (110/75 mm. Hg) and has remained normal. The urine sediment subsequently has included epithelial cells but no white blood cells or casts. Fig. 6 shows a postero-anterior radiograph of the abdomen 5 minutes after intravenous injection of dye. No dilatation was present. Additional studies revealed no evidence of vesico-ureteral reflux. Pathological examination of the diseased kidneys confirmed that they were both contracted by chronic puelonephritis (weighing 38 g. and 42 g.).

Discussion

The group at the Peter Bent Brigham Hospital have suggested that the prognosis for the transplanted kidney is considerably worse if the original disease is glomerulonephritis rather than pyelonephritis.

In two of their five recipient patients with glomerulonephritis, glomerulonephritis subsequently developed in the transplanted kidney. To avoid this, in a later patient, they did a nephrectomy 2 days before transplantation and removed the other diseased kidney at the time of transplantation (Murray et al. 1958).

In the present case open biopsy showed that the disease was pyelonephritis. Two diseased kidneys were therefore left in situ until the patient's health had improved 5 months later.

The transplanted kidney was not cooled, perfused, or subjected to anticoagulation. We considered that the delay and the intimal trauma with subsequent tendency to thrombosis that may be associated with manipulation of the kidney would decrease the chances of survival.

The kidney in this case had two renal veins and one renal artery. One of the two renal veins was short but wide and carried quite a large proportion of venous return, and yet vascular anastomosis was complete in 58 minutes. Clearly such a period of ischæmia does not preclude subsequent functional improvement, and, indeed, renal " hypertrophy " has seemingly been as great as that which occurs in a normal kidney remaining after nephrectomy. The mechanism of the delayed decrease in function is not known. It was thought at the time that one of the renal veins had thrombosed, but this now seems very unlikely. The change was probably due to a delayed secondary effect of ischæmia.

The behaviour of the hypertension in this patient after transplantation and, later, after bilateral nephrectomy was similar to that observed by Merrill (Merrill et al. 1956, Murray et al. 1958). The partial control of severe hypertension by the transplantation of undiseased kidney-tissue is best explained by the renoprival theory of Grollman et al. (1949) and Fasciolo's concept of the protective function of the normal kidney (see Braun Menendez 1958). Kolff (1958) has described a similar reduction in pressure in experimental renoprival hypertension in dogs after renal transplantation. It is not possible to say whether the antihypertensive effect of relatively normal kidney tissue is due to (*a*) the neutralisation of renin or angiotensin, or (*b*) the partial neutralisation of a humoral (but not necessarily vasoconstrictive) substance produced by an ischæmic kidney that tends to prevent normal maintenance of blood-pressure by normal kidney tissue (see Floyer 1957), or (*c*) the neutralisation of extrarenal hypertensive substances. The fact remains that malignant hypertension became mild after transplantation and disappeared after subsequent bilateral nephrectomy. It is probably significant that the blood-pressure rose on the 3rd to 10th post-transplantation days when the delayed depression of renal function occurred.

The administration of testosterone propionate in this case was probably the cause of considerable sodium retention preoperatively and also of voice changes and possibly changes in the hair subsequent to operation. It is also probable that without the testosterone the pre-operative uræmic state would have progressed more rapidly. In addition the hormone may promote and accelerate renal " hypertrophy " (Lattimer 1942, McKay 1940).

Summary

Renal transplantation was carried out between two identical twins. The recipient twin had bilateral chronic pyelonephritis.

The operation was completely successful despite an apparent decrease in function of the transplanted kidney shortly after the operation. The initially severe hypertension was very much improved after transplantation, and the blood-pressure reverted to normal after both diseased kidneys had been subsequently removed.

REFERENCES

Braun Menendez, E. (1958) *Circulation*, **17**, 719.
Dossetor, J. B., Morgen, R. O., Beck, J. C. (1960) Unpublished.
Floyer, M. A. (1957) *Brit. med. Bull.* **13**, 29.
Freedman, P., Spencer, A. G. (1957) *Clin. Sci.* **16**, 11.
Grollman, A., Muirhead, E. E., Vanatta, J. (1949) *Amer. J. Physiol.* **157**, 21.
Harris, S., Dossetor, J. B. (1959) *Canad. Nurse*, **65**, 508.
Kenyon, A. T., Knowlton, K., Sandiford, I., Koch, F. C., Letwin, G. (1940) *Endocrinology*, **26**, 26.
Kolff, W. J. (1958) *Circulation*, **17**, 702.
Lattimer, J. K. (1942) *J. Urol.* **48**, 778.
Masson, G., Corcoran, A. C., Page, I. H. (1949) *J. Lab. clin. Med.* **34**, 924.
McKay, E. M. (1940) *Proc. Soc. exp. Biol., N.Y.* **45**, 216.
Merrill, J. P., Murray, J. E., Harrison, J. H., Guild, W. R. (1956) *J. Amer. med. Ass.* **160**, 277.
Murray, J. E., Merrill, J. P., Harrison, J. H. (1958) *Ann. Surg.* **148**, 343.
Rapoport, S., West, C. D., Brodsky, W. A. (1949) *Amer. J. Physiol.* **157**, 363.

THE USE OF NORETHANDROLONE IN ACUTE RENAL FAILURE FROM OBSTETRIC CAUSES

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THE GENERAL INFIRMARY AT LEEDS

TESTOSTERONE is known to prolong the survival of nephrectomised rats because of its " protein sparing " activity (Masson et al. 1949). It has, therefore, been used in the treatment of acute renal failure, with variable but limited success (Dérot and Bernier 1950, Freedman and Spencer 1957). Merrill (1955) states that " testosterone propionate is a definite, but not all important, adjuvant to treatment " in acute renal failure, and he notes that the protein-sparing effect " wears off " in 10–14 days. In addition its virilising properties restrict its use in women.

Now that new steroids with less androgenic activity, which still promote protein anabolism or antagonise protein catabolism, have been synthesised their use has been suggested in the management of patients with acute

TABLE I—CLINICAL DETAILS OF NINETEEN PATIENTS WITH ACUTE RENAL FAILURE AFTER PREGNANCY

Case no.	Age (yr.)	Diagnosis	Parity	Week of gestation	Toxæmia	Surgery	Result
1	27	Postpartum toxæmia	2	40	Postpartum only	0	Recovered
2	39	Concealed accidental hæmorrhage	2	32	0	A.R.M.*	,,
3	38	,, ,, ,,	3	32	+	A.R.M.	,,
4	27	Abortion and hysterectomy	6	16	0	Hysterectomy	,,
5	21	Concealed accidental hæmorrhage	1	30	0	A.R.M.	,,
6	27	Abortion	4	13	0	Evacuation of uterus	,,
7	27	Eclampsia; pyelonephritis of right kidney; congenital cystic hypoplasia of left kidney	3	34	+	A.R.M.	Died
8	39	Concealed accidental hæmorrhage; cæsarean section	1	31	+	Cæsarean section	Recovered
9	30	Placenta prævia; cæsarean section and subtotal hysterectomy	4	34	0	Cæsarean section + subtotal hysterectomy	,,
10	22	Concealed accidental hæmorrhage; cortical necrosis	1	32	+	A.R.M.	Died
11	28	,, ,, ,, ,, ,,	1	33	+	A.R.M.	,,
12	26	Pre-eclampsia with severe hepatitis	2	35	+	A.R.M.	Recovered
13	37	Concealed accidental hæmorrhage	1	30	0	A.R.M.	,,
14	36	,, ,, ,,	5	31	+	A.R.M.	,,
15	27	Concealed accidental hæmorrhage; cæsarean section; cortical necrosis	1	32	Pre-existing hypertension	Cæsarean section	Died
16	17	Concealed accidental hæmorrhage	1	34	Acute	A.R.M.	Recovered
17	34	,, ,, ,,	6	32	0	A.R.M.	,,
18	43	Concealed accidental hæmorrhage; cortical necrosis	6	32	+	0	Died
19	22	Chronic pyelonephritis; concealed accidental hæmorrhage; cortical necrosis	1	30	0	0	,,

*A.R.M.=artificial rupture of membranes.

renal failure. Norethandrolone, or 17 α-ethyl-17-hydroxy-19-nor-androst-4-en-3-one, is one such compound which in man has potent anabolic activity (Spencer et al. 1957) and yet in laboratory animals is reported to be only 6% as androgenic as testosterone (Saunders and Drill 1957, 1958). In a preliminary communication in 1958 McCracken and Parsons described the effects of norethandrolone in patients with acute renal failure. This compound depressed considerably the rate of urea formation in six patients with acute renal failure due to obstetric causes, and its effect was similar but less in three of five patients with acute renal failure unassociated with pregnancy. Boen (1959) has commented that, although the results were encouraging, definite conclusions could not be drawn because the number of cases was small.

We have now investigated in detail nineteen obstetric patients with acute renal failure (including those already reported). In sixteen of these the action of norethandrolone, testosterone, methyl testosterone, or progesterone was observed, the other three acting as controls.

The Investigation

The Patients

Table I shows details of the nineteen patients studied and their diagnoses. All developed acute renal failure following complications of pregnancy, and they were transferred to the General Infirmary at Leeds because they might require hæmodialysis. As infection is known to increase the rate of protein catabolism no infected patient was chosen for investigation.

Conditions of Study

From the time of admission all patients were given by mouth a standard daily regime of glucose 100 g. and vitamins in 400 ml. of water. This achieved a daily weight-loss of 300–400 g. Sensible loss of water was replaced as it occurred.

A modified Kolff-Brigham rotating-coil artificial kidney was used for hæmodialysis, the indications being those of Parsons and McCracken (1959).

The three control patients (table I, cases 1–3) did not have steroids, whilst the remaining sixteen (cases 4–19), after a preliminary control period of 3–5 days, were given a course of the steroid under investigation, for 4–5 days. In some patients a further course of one or more of these steroids was given over the next few days. The drugs were given by mouth or by injection, in divided doses throughout the day.

Protein catabolism was estimated by calculation of the 24-hour urea production. Urine was collected in 24-hour periods from 9 A.M., and blood was taken for analysis between 9 A.M. and 10 A.M. each day. Urea in plasma and urine was estimated by the method of Archibald (1945). Fæces were not collected, as the fæcal loss of nitrogen is relatively constant and independent of intake (Dempsey et al. 1958). Lochia was not analysed because the investigations were made during the later puerperium. The daily urea production was obtained from the sum of the daily accumulation of urea in the total body-water and the daily excretion of urea in the urine if this was formed. The accumulation in the total body-water was calculated by multiplying the daily rise in the plasma-urea level by the patient's total body-water, assumed to be 60% of the patient's weight as recorded at the start of the investigation. Any error in calculating the total body-water by this means will be constant for each patient and will not affect the result significantly. Furthermore, as the total body-water was decreasing day by day, any reduction in urea production resulting from steroid therapy would be greater than that calculated.

Results

Controls

Fig. 1 shows the results in a patient (case 2) who had oliguria for 23 days. The rate of rise of plasma-urea remained relatively constant throughout this period. Similar results were obtained in the other two control patients (cases 1 and 3).

Effect of Norethandrolone

Table II shows the mean daily rate of urea production in the nineteen patients during the control period. Fourteen of these were later given norethandrolone, which resulted in an average depression of urea production of 70%. In six patients

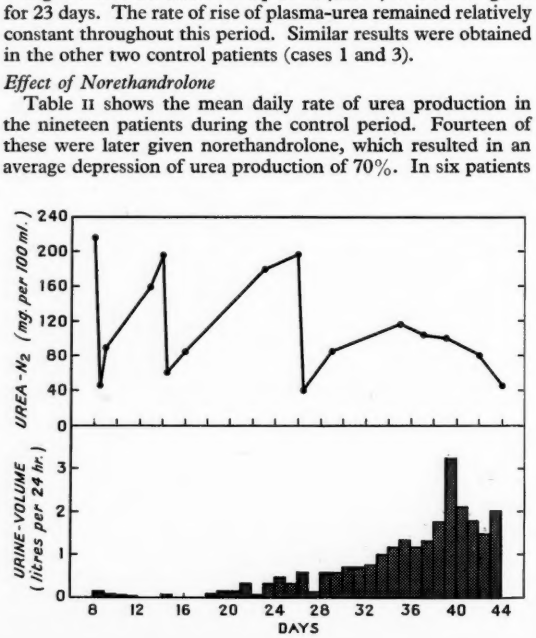

Fig. 1—Daily plasma urea-N_2 level and urine output in a control patient (case 2) not given steroids.

TABLE II—EFFECT OF NORETHANDROLONE ON THE DAILY FORMATION OF UREA (AVERAGE OF 4–5 DAYS)

Case no.	Control average daily urea production (in g. N_2)	Dose of norethandrolone (daily)	Average daily urea production with norethandrolone	% reduction in urea formation
1	5·3	0	..	..
2	4·2	0	..	..
3	7·2	0	..	..
4	9·1	80 mg. orally	1·8	81
5	6·4	80 mg. orally	2·1	67
6	4·1	80 mg. orally	0·2	95
7	8·4	100 mg. i.m.*	4·1	51
8	6·3	100 mg. i.m.	2·0	68
9	4·3	80 mg. orally	1·9	56
10	5·5	0	..	..
11	7·1	30 mg. orally	2·6	63
12	8·0	30 mg. orally	3·6	55
13	8·7	30 mg. orally	2·8	68
14	7·4	30 mg. orally	3·0	59
15	9·5	30 mg. orally	3·1	66
16	6·1	30 mg. orally	1·2	80
17	8·0	50 mg. i.m.	0·0	100
18	6·0	0	..	..
19	7·2	30 mg. orally	2·4	67

* i.m. = intramuscular.

who had 80 or 100 mg. of norethandrolone daily the average depression was 70%, and in seven patients who had 30 mg. daily it was 65%. In all cases there was a lag of about 24 hours before the full effect of norethandrolone was evident.

Fig. 2 shows the results in a patient (case 8) who was given 100 mg. of norethandrolone daily by intramuscular injection after a control period of 3 days. The rate of urea production was reduced from 6·3 to 2·0 g. per day (68%). This reduction started suddenly 24 hours after norethandrolone was first given.

Effect of Testosterone and Methyl Testosterone

Three patients (cases 10, 11, and 15) were given testosterone propionate 50 mg. twice daily by injection, and one (case 16) was given methyl testosterone 50 mg. 6-hourly by mouth. The results are shown in table III. In case 11 the urea production increased. In the other three patients (cases 10, 15, and 16) the average depression of urea production was 37%, and in only one (case 10) did its effectiveness approach that of norethandrolone (fig. 3). This patient seemed to "escape" from the effect about 3 days after testosterone was withdrawn. Fig. 4 shows the results in case 15. When testosterone propionate 50 mg. was given twice daily by injection the rate of urea formation was reduced by 25%, but when norethandrolone 30 mg. daily was given by mouth the reduction was increased to 66%.

Effect of Progesterone

Two patients (cases 17 and 18) were given progesterone 100 mg. twice daily by injection (table III). Urea production was depressed by 24% and 22% respectively. The effect on case 18 is shown in fig. 5.

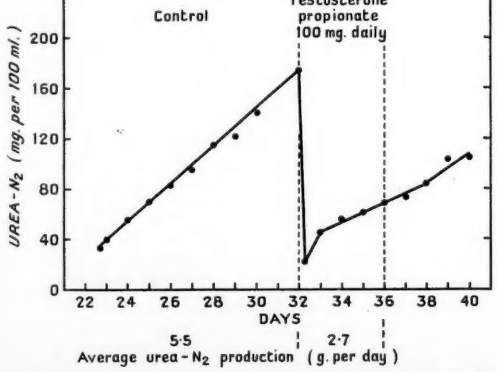

Fig. 3—Effect of testosterone propionate on the rise of plasma urea-N_2 in case 10.

Effect of Methyl Testosterone and Progesterone

This combination was studied in two patients (cases 16 and 18) who were given methyl testosterone 50 mg. 6-hourly by mouth, and progesterone 100 mg. twice daily by intramuscular injection. The results are shown in table III. Urea production was reduced by 64% and 66% respectively. Figs. 5 and 6 show the results in these patients. Case 16 (fig. 6) had 50 mg. of methyl testosterone 6-hourly by mouth initially for 4 days, which decreased the urea production by 36%. The same dose of methyl testosterone was continued for 4 more days together with 100 mg. of progesterone twice daily by injection. The rate of urea production decreased by a further 28% of the original rate. After this she was given norethandrolone 30 mg. daily by mouth. This caused further reduction of urea production to 80%, but fig. 6 shows a 48-hour time-lag before the effect of adding progesterone to methyl testosterone became apparent, and in actual fact a combination of methyl testosterone and progesterone seemed to be as effective as norethandrolone.

Fig. 5 shows the results in case 18. This patient had progesterone at first with a 22% reduction of urea production, but when methyl testosterone was added the reduction was increased to 66%. The graph also shows the escape from the effect of steroids after 5 days.

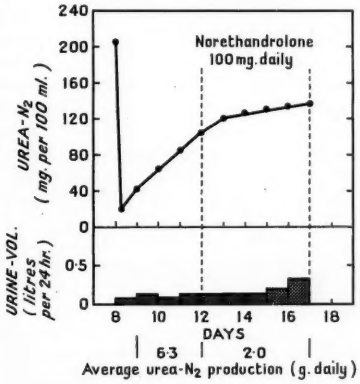

Fig. 2—Effect of norethandrolone 100 mg. by injection on the rise of plasma urea-N_2 in case 8.

Thus, while progesterone causes a depression of urea production, and methyl testosterone has a somewhat greater effect, the two drugs together produce an effect similar to that of norethandrolone.

Side-effects of Norethandrolone

The two theoretically important side-effects of norethandrolone are virilisation and jaundice. In addition to the fourteen cases studied above we have treated with norethandrolone eleven cases of acute renal failure from obstetric causes. In none of these 25 patients has any side-effect been observed. One patient (case 12) had severe toxæmia of

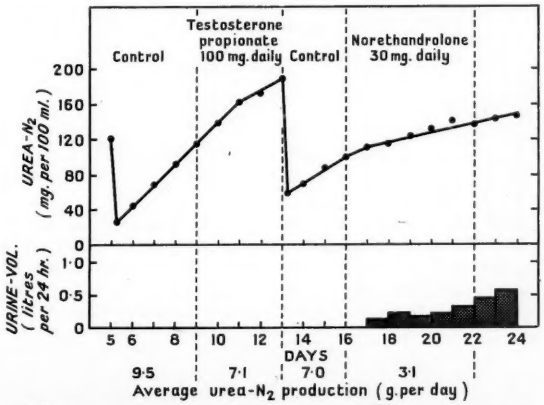

Fig. 4—Comparison of the effects of testosterone propionate by injection and norethandrolone by mouth in case 15.

TABLE III—THE EFFECT OF TESTOSTERONE, METHYL TESTOSTERONE, PROGESTERONE, OR A COMBINATION OF METHYL TESTOSTERONE AND PROGESTERONE ON THE DAILY FORMATION OF UREA (AVERAGE OF 4–5 DAYS)

Case no.	Control average daily urea production (in g. N_2)	Daily dose of testosterone	Average daily urea production on testosterone	% reduction in urea formation	Daily dose of progesterone	Average daily urea production on progesterone	% reduction in urea formation	Daily dose of methyl testosterone and progesterone	Average daily urea production on methyl testosterone and progesterone	% reduction in urea formation	Daily dose of norethandrolone	Average daily urea production on norethandrolone	% reduction in urea formation
10	5·5	Testosterone propionate 100 mg. i.m.*	2·7	51	..	..	..	..	..	..	..	..	..
11	7·1	Testosterone propionate 100 mg. i.m.	10·3	+45	..	..	..	..	..	..	30 mg. orally	2·6	63
15	9·5	Testosterone propionate 100 mg. i.m.	7·1	25	..	..	..	..	..	..	30 mg. orally	3·1	66
16	6·1	Methyl testosterone 200 mg. orally	3·9	36	..	..	..	200 mg. of each	2·2	64	30 mg. orally	1·2	80
17	8·0	..	..	..	200 mg. i.m.	6·1	24	..	..	..	50 mg. i.m.	0·0	100
18	6·0	..	..	..	200 mg. i.m.	4·7	22	200 mg. of each	2·0	66	..	..	..

* i.m. = intramuscular

pregnancy with gross liver damage and signs of impending hepatic coma before treatment, but these changes subsided uneventfully during administration of norethandrolone.

In cases of acute renal failure treatment with norethandrolone is unlikely to last longer than 3 weeks. As both virilisation and jaundice take some time to develop we do not think that the use of norethandrolone in acute renal failure imposes a significant hazard.

Duration of Effect

Figs. 3 and 5 show an escape from the effects of testosterone and a combination of methyl testosterone and progesterone 3–5 days after treatment is stopped. Similar results have been found with norethandrolone by Schedl et al. (1959) in normal subjects. We have not been able to demonstrate an escape after withdrawing norethandrolone. The maximum effect, however, certainly lasted at least 2–3 days after norethandrolone was stopped but further observation was impossible, either because renal function was recovering or because the patient deteriorated and died—a previous percutaneous renal biopsy having confirmed the presence of complete cortical necrosis.

Discussion

Incidence of Acute Renal Failure in Pregnancy

The commonest cause of acute renal failure in later pregnancy is concealed accidental hæmorrhage, which is said to occur in 0·5–0·6% of all deliveries (Sheehan and Moore 1952, Sexton et al. 1950). Sheehan and Moore reported seventy-five deaths in 115,000 deliveries, of whom forty-four died of renal failure in the puerperium or died on the day of delivery, showing severe renal damage post mortem. These patients (0·04%) probably represent those with complete cortical necrosis or other extensive renal damage, but anything up to half of the cases of concealed accidental hæmorrhage may have had some degree of renal impairment—an incidence of about 0·3% of deliveries.

Less than 10% of these patients are likely to have complete cortical necrosis, and it is therefore important that life should be supported long enough to allow possible recovery of renal function. As many patients with acute renal failure from concealed accidental hæmorrhage have not shown signs of recovering renal function for up to 3 weeks we have not performed diagnostic procedures, such as retrograde pyleography and percutaneous renal biopsy, until after this time had elapsed. During the period of supportive management the use of norethandrolone has reduced the necessity for dialysis, and several cases have recovered without the use of the artificial kidney.

In other conditions causing acute renal failure associated with pregnancy, such as hæmorrhage from placenta

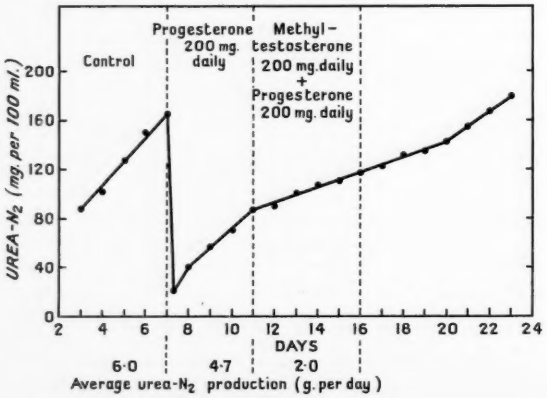

Fig. 5—Effect of progesterone and of a combination of progesterone and methyl testosterone in case 18.

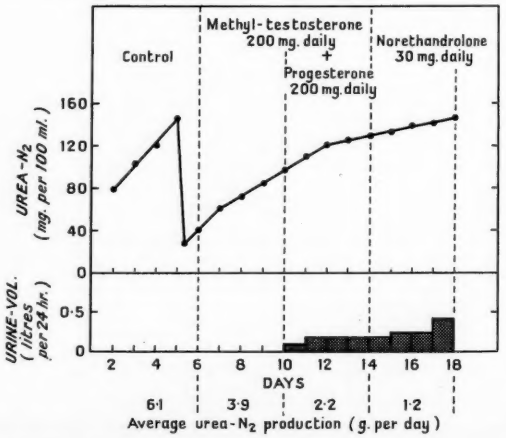

Fig. 6—Effect of methyl testosterone, of methyl testosterone and progesterone, and of norethandrolone in case 16.

prævia and abortion, we have found norethandrolone equally effective.

Reduction in Protein Catabolism

It is generally agreed that the symptoms of acute renal failure are due to accumulation of the products of protein breakdown. With a diet composed solely of carbohydrate, the rate of protein breakdown is said to be reduced to a minimum (Gamble 1947, Munro 1951). Urea is a convenient marker for the rate of protein breakdown, although its role in producing the clinical effects of uræmia is uncertain. Factors other than diet affect the rate of protein breakdown, and in pregnancy the metabolism of protein appears to be modified.

Poo et al. (1940) showed in the rat that during pregnancy on an adequate protein intake the total quantity of body protein formed is higher than in normal rats on a similar diet, and that the largest proportion of this protein is laid down in the liver. Venning et al. (1959) have shown a negative nitrogen balance for at least 10 days after parturition. In postpartum renal failure this will increase the rise of plasma-urea. Thus any measure is of value which will reduce the rate of protein breakdown so that toxic levels are not reached before urine output is re-established. The necessity for and frequency of hæmodialysis will consequently be reduced in the more severe cases, and more patients could be managed in hospitals where there are no facilities for hæmodialysis. By reducing the need for starvation, it should lessen the morbidity and shorten the period of convalescence.

In the fourteen cases which were given norethandrolone, the average reduction of protein breakdown was about 70%. The effect on protein breakdown of norethandrolone 30 or 80 mg. daily by mouth, or 50 or 100 mg. by intramuscular injection, is of the same order. For practical purposes 30 mg. of norethandrolone by mouth or 50 mg. by injection daily appears to achieve the greatest effect within 24 hours of first starting the drug, and the effects persist for several days after a course lasting 4–5 days. We have not determined the optimum period of treatment. In addition to the effect on protein breakdown the changes in other chemical indices of uræmia are slowed down to more or less the same degree.

Norethandrolone is more effective than either methyl testosterone or progesterone alone, and at least as effective as a combination of these two drugs; but, perhaps of greater importance, it acts more quickly. We therefore recommend that norethandrolone be used routinely in the management of acute renal failure associated with pregnancy.

Mode of Action

The mechanism of action of norethandrolone is unknown. There is no obvious correlation with the cause of renal failure except that it has more effect in patients with acute renal failure associated with pregnancy. We have also seen a response in some patients with acute renal failure associated with nephritis, and in patients with traumatic uræmia, but this is often masked by the severe catabolic stresses of infection and other complications. Gjørup and Thaysen (1958) too have found that patients with chronic renal failure respond to norethandrolone.

The greater effect of norethandrolone in patients with renal failure associated with pregnancy is unlikely to be due to inhibition of uterine involution. Two of our patients, who had hysterectomies performed at the onset of renal failure, still showed the typical response. Whether the progestational effects of norethandrolone have any great bearing on its anticatabolic activity is uncertain. In two patients progesterone appeared to have some anticatabolic activity; this contrasts with the findings of Landau et al. (1958), who showed that progesterone, and other progestational compounds with a C_{17} side-chain in the beta position, usually had a catabolic effect in non-pregnant women. Possibly during the puerperium progesterone itself is anticatabolic, and the so-called anabolic steroids may be more effective in patients at this time.

Summary

The effect of certain steroids on patients with acute renal failure after pregnancy has been studied.

Norethandrolone can reduce the rate of urea production by up to 70% in these patients. This is significantly more than the effect of either testosterone or progesterone alone, and is at least as great as the effect of a combination of these two drugs.

The mechanism of action of the so-called anabolic steroids remains uncertain, but they may in fact be anticatabolic.

It is suggested that norethandrolone be used routinely in the treatment of prolonged oliguria or anuria following pregnancy, because this will reduce the necessity for and frequency of hæmodialysis.

We wish to thank Mrs. S. M. Hobson, A.M.I.L.T., for the chemical estimations, and Messrs. G. D. Searle & Co. for supplies of ' Nilevar '.

REFERENCES

Archibald, R. M. (1945) *J. biol. Chem.* **157**, 507.
Boen, S. T (1959) Peritoneal Dialysis. Netherlands.
Dempsey, E. F., Carroll, E. L., Albright, F., Henneman, P. H. (1958) *Metabolism*, **7**, 108.
Dérot, M., Bernier, J. J. (1950) *Bull. Soc. méd. Hop. Paris*, **66**, 205.
Freedman, P., Spencer, A. G. (1957) *Clin. Sci.* **16**, 11.
Gamble, J. L. (1947) *Harvey Lect.* **42**, 247.
Gjørup, S., Thaysen, J. H. (1958) *Lancet*, ii, 886.
Landau, R. L., Lugibihl, K., Dimick, D. F. (1958) *Ann. N.Y. Acad. Sci.* **71**, 588.
Masson, G. M. C., Corcoran, A. C., Page, I. H. (1949) *J. Lab. clin. Med.* **34**, 925.
McCracken, B. H., Parsons, F. M. (1958) *Lancet*, ii, 885.
Merrill, J. P. (1955) The Treatment of Renal Failure. New York.
Munro, H. N. (1951) *Physiol. Rev.* **31**, 449.
Parsons, F. M., McCracken, B. H. (1959) *Brit. med. J.* i, 740.
Poo, L. J., Lew, W., Lee, D. D., Addis, T. (1940) *J. Nutrition*, **19**, 505.
Saunders, F. J., Drill, V. A. (1957) *Proc. Soc. exp. Biol. N.Y.* **94**, 646.
— — (1958) *Metabolism*, **7**, 315.
Schedl, H. P., Delea, C., Bartter, F. C. (1959) *J. clin. Endocrin.* **19**, 921.
Sexton, L. I., Hertig, A. T., Reid, D. E., Kellogg, F. S., Patterson, W. S. (1950) *Amer. J. Obstet. Gynec.* **59**, 13.
Sheehan, H. L., Moore, H. C. (1952) Renal Cortical Necrosis. Oxford.
Spencer, H., Berger, E., Charles, M. L., Gottesman, E. D., Lazlo, D. (1957) *J. clin. Endocrin.* **17**, 975.
Venning, E. H., Dyrenfurth, I., Lowenstein, L., Beck, J. (1959) *ibid.* **19**, 403.

PASTEURELLA SEPTICA IN CHRONIC NASAL SINUSITIS

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IN 1945 a strain (AW) of *Pasteurella septica* was isolated from a farmer with frontal sinusitis (Bartley and Hunter 1947).

Case-record

This patient was first seen in 1943 when a right middle turbinectomy was performed; but because of persistent frontal headache and a greenish purulent nasal discharge a right radical external fronto-ethmoidal operation was done in 1945 combined with penicillin therapy. At this operation no involvement of bone was noted. The patient remained well until 1954, when he developed intermittent swelling round his right eye and a greenish right-sided nasal discharge. These symptoms continued until 1958 when he was again referred to Mr. Kennedy Hunter. X-ray examination showed opacities of both antra and of the right frontal sinus, and blood and pus

were found in the right antrum on exploratory puncture. In January, 1959, a right external frontal operation showed extensive involvement of the bony septa between the sinuses and infection of the frontal and maxillary bones. After operation the patient was discharged without symptoms, but when he was seen ten months later he was again complaining of swelling round his right eye suggesting the persistence of infection.

Bacteriology

In January, 1959, a second strain (AW/59) of *Past. pestis* was isolated from pus taken at operation. Unfortunately the AW strain isolated in 1945 had not remained viable and it was impossible to make a direct comparison of the two strains. They were, however, similar in morphological, cultural, and biochemical properties apart from a few minor differences: for example, strain AW grew on MacConkey's medium while AW/59 did not; and the AW strain was sensitive to penicillin while the AW/59 strain was resistant. The AW/59 strain was also resistant to sulphathiazole but sensitive to all other antibiotics against which it was tested.

Using the criteria of Smith (1959) it is not possible to assign AW/59 to an animal source. Thus capsules were present, colonies were not mucoid, hyaluronic acid was produced, iridescence was not seen, and acid agglutinability was present at pH 2·5 and 3·5 but not at pH 4·5 or 5·0. The organism was pathogenic for mice, and it produced fermentation of xylose and mannitol but not sorbitol, maltose, or trehalose.

An agglutination test using immune rabbit sera was carried out as previously described (Bartley and Hunter 1947) with the following results:

Strain	*Titre of rabbit antisera to AW/59 strain*		
	Unabsorbed	*Absorbed by AW/59 strain*	*Absorbed by 1737 strain*
AW/59	1 : 1280	<1 : 5	1 : 80
Nat. Type Cult. no. 1737..	1 : 1280	1 : 80	1 : 80

It would appear, therefore, that AW/59 and the National Type culture strain no. 1737 are serologically related but not identical. A similar conclusion was reached when the AW strain was compared with 1737 in 1945.

Blood taken from the patient in November, 1959, had an agglutination titre of 1 : 40 against the AW/59 strain. In 1945 the patient's serum had no demonstrable antibody—which is not an unusual finding in *Past. septica* infections.

Discussion

Human infections with *Past. septica* are uncommon, and the few reported cases of sinus infection with this organism appear to have run very chronic courses. Hadorn (1938) recorded a case of *Past. septica* meningitis eight months after a fracture of the skull involving a presumably infected right frontal sinus, and Bezjak and Mimica (1952) described a patient with *Past. septica* sinus infection who had symptoms and a greenish nasal discharge for six years. It is unfortunately impossible to exclude reinfection in the present case, but it seems equally reasonable to assume a chronic infection over a period of at least twelve years. Apart from the change in penicillin sensitivity, the AW and AW/59 strains appear to be very similar.

Summary

A strain of *Past. septica* was isolated from a patient with frontal sinusitis in 1945 and again in 1959.

Direct comparison of the two strains has not been possible, but they appear to be essentially similar except in certain biochemical properties and in penicillin sensitivity.

Assuming that reinfection did not occur, *Past. septica* sinusitis may apparently be very chronic and last for as long as fifteen years.

I wish to thank Prof. G. W. A. Dick and Mr. Kennedy Hunter for cooperation and help in the preparation of this paper, and Mr. T. Connor for technical assistance.

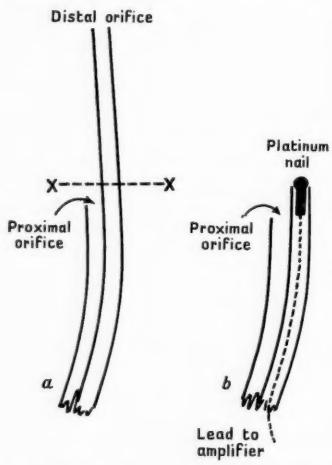
REFERENCES

Bartley, E. O., Hunter, K. (1947) *Lancet*, **i**, 908.
Bezjak, V., Mimica, M. (1952) *Brit. med. J.* **ii**, 757.
Hadorn, W. (1938) *Schweiz. Med. Wschr.* **68**, 665.
Smith, J. E. (1959) *J. comp. Path.* **69**, 231.

New Inventions

A MULTIPURPOSE CARDIAC CATHETER

THE standard cardiac catheter has a lumen through which pressure pulses and blood samples may be obtained, and injections may be made. For recording intracardiac electrocardiograms a catheter is necessary with an electrode near its tip. When inhaled hydrogen is used to detect left-to-right intracardiac shunts a catheter bearing a platinum-black electrode is necessary.[1] The investigation of patients with congenital heart-disease has been simplified by using a catheter capable of serving each of these purposes.



(*a*) Section through the double-lumen cardiac catheter. The distal portion is amputated at ×——×, 1 cm. from the proximal orifice. (*b*) Section showing the platinum nail inserted into the cut end of the catheter, and connected to an amplifier by a lead lying in one lumen of the catheter.

The distal portion of a double-lumen catheter is amputated at ×—× (see figure). A platinum nail, cemented into the cut end, is connected by a lead running through the lumen to a suitable amplifier. The platinum nail is "blacked" by electrolysis. The finished catheter thus bears at its tip the orifice of one lumen, and the platinum-black electrode. The electrode may be used for recording the intracardiac electrocardiogram, or for detecting inhaled hydrogen.

In practice the catheter is inserted into the right side of the heart and pulmonary artery. Pressures are recorded through the lumen. Left-to-right shunts are detected and localised by hydrogen inhalation. Right-to-left shunts are revealed by indicator-dilution curves after dye has been injected through the lumen of the catheter. The intracardiac electrocardiogram is recorded when necessary.

The catheter may be obtained from Messrs. Chas. F. Thackray, 10, Park Street, Leeds, 1. We are indebted to Mr. H. Womack, F.I.S.T., of the department of physical chemistry in the University of Leeds, for overcoming the problem of providing a cardiac catheter with a platinum-black electrode.

H. M. S. was in receipt of a grant from the Nuffield Foundation.

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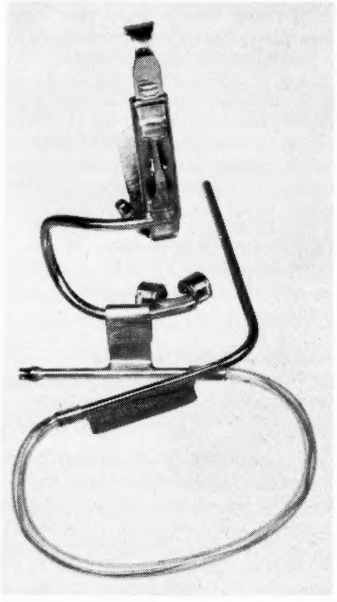
1. Clark, L. C., Jr., Bargeron, L. M., Jr. *Surgery*, 1959, **46**, 797.

A SUCTION TUBE FOR USE DURING TONSILLECTOMY AND ADENOIDECTOMY

THE suction tube designed by Sidney Yankauer (1872–1932) of New York, when he was laryngologist at Mount Sinai Hospital, was brought into use with the guillotine operation and the hurried adenoidectomy performed with the patient on his side.

Many surgeons, however, have now adopted dissection tonsillectomy preceded or followed by a more leisurely adenoidectomy.



Under direct vision the distal curve of the Yankauer instrument is unnecessary and obscures the view. A straight shaft is needed in order to apply the end to the point seen. The bulbous end is a safeguard if the instrument is used blindly, but is cumbersome when used during dissection.

The instrument is made with a light handle angled at 90°, to be held in the reverse grip of the left hand. The shaft is a straight tube with a round hole at each side $^1/_8$ in. from the open extremity. This arrangement reduces the hissing heard when the sucker is in use. The handle end is connected by a 15 in. flexible plastic tube to an adaptor hanging by a flat hook from the arch of a Boyle-Davis gag. To the large end of this adaptor the usual pressure tube from the suction pump is attached. This hooked adaption prevents the instrument from falling to the floor if unattended.

Messrs. Allen & Hanburys, Bethnal Green, London, E.2, have produced this suction tube in stainless steel with a transparent tube made by Portex Plastics. Mr. G. A. Cook took the photograph.

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A RECTAL IRRIGATOR

RECTAL irrigation with a 1 in 500 solution of mercuric perchloride, to destroy free carcinoma cells in the bowel lumen, during anterior resection for carcinoma is now well established.[1]

The usual method of irrigation is by means of a large-bore rubber tube or catheter introduced through a proctoscope when the bowel clamp is in place before the anastomosis. This procedure entails disturbing the towelling, and interrupting the operation to some extent. To avoid this disturbance, a self-retaining double-lumen rubber catheter has been found useful, and has the advantage that large quantities of the irrigating solution can easily be washed through the rectum. The physical removal of free carcinoma-cells complements their chemical destruction by the irrigating fluid.

The irrigator (see figure) comprises a stiff red rubber tube 14 in. long, with a $^1/_2$ in. lumen, and with two side-holes $^1/_2$ in. long just behind the tip. The inlet catheter is $^1/_4$ in. wide and projects 2 in. beyond the main tube. The self-retaining inflatable bag (see inset) of translucent rubber and 25 ml. capacity is situated $1^1/_2$ in. behind the tip of the irrigator, and has a pilot bag. The whole instrument can be sterilised by boiling.

Before the operation begins the irrigator is inserted into the rectum, and the self-retaining bag is inflated. After the distal bowel clamp is in place, irrigation can proceed without interrupting the operation. The irrigating solution drains via the main tube into a suitable receptacle without contaminating the patient or the assistants.

The irrigator has been constructed by Messrs. J. G. Franklin & Sons Ltd., 51, Manchester Street, Portman Square, London, W.1.

I am grateful to Mr. E. C. Butler and Mr. R. P. Warren for help and advice.

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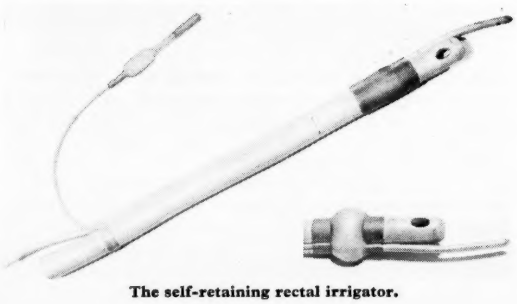
1. Goligher, J. C., Dukes, C. E., Bussey, H. R. *Brit. J. Surg.* 1951, **39**, 194.



The self-retaining rectal irrigator.

Reviews of Books

Coloured Immigrants in Britain

J. A. G. GRIFFITH, JUDITH HENDERSON, MARGARET USBORNE, DONALD WOOD. London: Oxford University Press, for the Institute of Race Relations. 1960. Pp. 225. 25*s*.

THIS useful book brings together much of the material written in recent years about coloured immigrants. It includes an analysis of the facts and figures known to local authorities and voluntary welfare organisations; a summary and assessment of the existing sociological work on the subject; a statement of the attitudes of the Government, the political parties, the trade unions, and other bodies; a discussion from the legal standpoint of the existing law and of measures, such as the restriction of immigration and deportation of undesirable persons, that have been proposed; and a summary of the experience of the United States in such matters as housing and employment.

Information was obtained from local-government and other officials by means of a long questionary, including specific questions on employment, housing, and health matters; and research-workers reported on visits to thirty-two centres of coloured population. It has been impossible to publish the summaries of statistical material and opinions, but the information is available for inspection in the Institute of Race Relations.

In the past ten years large numbers of West Indians, West Africans, Indians, and Pakistanis have immigrated to Britain, and in December, 1958, the coloured population from the Commonwealth was reported to be about 210,000. At the time of this survey economic conditions in the West Indies had improved and propaganda measures by West Indian Governments, explaining to prospective immigrants the difficulties of work and accommodation in Great Britain, seemed to have slowed the flow; but in the first six months of 1960 many West Indians were still arriving in this country. Immigrants from India and Pakistan come from rural areas and are separated from the white population in their home country by barriers of religion, language, and culture and show little desire to mix with the British people. Other migrant workers from Africa have come to this country as seamen in the past hundred years but have recently moved inland from the ports where they originally lived.

London has far the largest coloured population (90,000) but estimates of the population vary widely in all areas where

coloured people have recently settled. The other main centres of population were at the time of the survey said to be Birmingham (25,000–30,000), Liverpool and Manchester (8000–10,000), Nottingham (4000–5000). Most of the immigrants are men between 20 and 45 and only about 10% of the Indians and Pakistanis and 20–30% of the West Indians are women. Mixed marriages are uncommon except in old-established coloured communities, but semi-permanent or temporary liaisons between coloured men and white women are not unusual, and white women, both married and unmarried, play a steadying and fostering part among recent arrivals. Coloured children seem to meet no serious difficulties in the schools, although special classes have sometimes been organised for pupils handicapped by an imperfect knowledge of English. But when coloured children leave school "they leave a cosy world where they are judged by their skill at games or the colour of their blazer and enter the adult world where the colour of their skin may be important".

The greatest problem facing the coloured immigrants is to find a home, and most of them live in poor working-class areas in large Victorian terrace houses that are dilapidated and unsatisfactory if not actually due for clearance. Most coloured workers are in unskilled jobs and many are employed in very hot and humid conditions. Others work as pedlars, in public transport, and in restaurants.

Studies by Springett and others on the higher incidence of pulmonary tuberculosis in immigrants from Asia seem to be confirmed by the rather patchy statistics collected during the survey. The findings of Willcox on the increased incidence of gonorrhœa amongst immigrants, especially West Indians, are noted. The available evidence shows that very few coloured people, whatever their nationality, go into mental hospitals and the number who commit suicide is extremely small.

A Bibliography of Internal Medicine

Selected Diseases. ARTHUR L. BLOOMFIELD, M.D., professor of medicine emeritus, Stanford University. Chicago: University of Chicago Press. London: Cambridge University Press. 1960. Pp. 312. 48*s*.

Professor Bloomfield, puzzled by the difficulty of arousing serious interest in the historical side of medicine, blames the conventional method of treating the subject, and the inaccessibility of the important papers. To remedy this he published two years ago a selected bibliography of important contributions on communicable diseases, with extracts and critical comments. In the present volume he applies the same technique to twenty-one diseases "of old and honourable lineage." He has tried to list every reference of fundamental importance in the development of each, with appropriate excerpts for the benefit of the reader who does not have access to the originals or who has difficulty with French or German. The diseases are what one would expect, with the exceptions of chlorosis and trichinosis; and it is odd, since the volume is intended especially for students, that he plays down Paget's discovery of the parasite while he was a preclinical student at Barts. Dealing with diabetes mellitus and subacute bacterial endocarditis, he abstracts at some length twenty-one and twelve important papers respectively with detailed references. Like its predecessor this is a valuable source-book that is likely to stimulate further reading.

Florence Nightingale's Nurses: the Nightingale Training School

LUCY SEYMER. London: Pitman Medical Publishing Co. 1960. Pp. 169. 20*s*.

JUST a hundred years have gone by since the "Nightingale School" was opened, and the centenary has been appropriately marked by this account of its development. The school had its origin in a public subscription raised in Florence Nightingale's honour in 1855, while she was working in the Crimea. The fund eventually contained £44,000, and it is noteworthy that a fifth of this total was contributed from barracks, messes, and even the front line, by all ranks of the Army. This money was used, under the direction of a small council nominated by Miss Nightingale herself, to train probationers at St. Thomas's Hospital.

Fifteen nurses initiated the scheme, and, though the size of the school increased, its eventual influence on nursing all over the world was not derived from the mere number of its pupils. It sprang rather from a stipulation in the earliest days that the trainees might subsequently take posts only in approved hospitals—that is to say, ones in which they would be permitted to introduce the standards and methods of the parent institution itself.

The Nightingale Training School may be a hundred years old, but it is interesting to note how many of its basic principles still endure as cornerstones of nursing today. (These include the concept of a matron having absolute responsibility for the nursing staff: the rendering of periodic reports by each sister on the student nurses in her ward; and the importance attached to all probationers living together, and in a home, the better to learn order and discipline.) Mrs. Seymer's book, then, is important not only because it is the story of a small body of carefully selected women but also because it deals, in a very engaging fashion, with the antecedents of every nurse who works in our wards today.

The Structure and Dynamics of the Psyche

C. G. JUNG. *Collected works*. Vol. VIII. Editors: Sir HERBERT READ, MICHAEL FORDHAM, M.D., GERHARD ADLER, PH.D. Translated by R. F. C. HULL. London: Routledge & Kegan Paul. 1960. Pp. 596. 42*s*.

THIS volume contains eighteen papers setting out Jung's dynamic concepts from the time of his divergence from Freud's psychoanalytical theories to the present time. There are seven sections, containing papers grouped together according to theme. The opening paper, On Psychic Energy, expounds and clarifies Jung's libido theory, and the final section is occupied by his concept of synchronicity, "an acausal connecting principle". In this long paper, analytical psychology is linked with such apparently unrelated fields as modern physics, astrology, extrasensory perception, and statistics, in a closely reasoned argument.

Dew-Line Doctor

GARETH HOWERD. London: Robert Hale. 1960. Pp. 191. 18*s*.

THE Distant Early Warning Line is a chain of radar stations running, roughly, from the most westerly part of Alaska to the east of Baffin Island. Its purpose, like that of the Pinetree and the Mid-Canada lines, which lie south of it, is to give the cities of North America some warning of any aerial attack coming from the direction of the North Pole. The construction and maintenance of the line has posed, among other problems, that of the medical care of many small groups of men, living hundreds of miles apart under conditions of utter desolation. Gareth Howerd was, for a year, one of those who have overcome this difficulty by the use of aircraft and radio, along lines reminiscent of the Australian Flying Doctor service but in a very different climate.

His book is for general readers, and his colleagues may regret an absence of clinical detail in the descriptions of the diseases he met. But his writing recalls Grenfell's stories of the Labrador, and reads just as fascinatingly.

Neurology (5th ed. Oxford: Blackwell Scientific Publications. 1960. Pp. 1386. 196*s*.).—The latest edition of this well-known textbook by Dr. R. R. Grinker, Prof. P. C. Bucy, and Prof. A. L. Sahs amply maintains the reputation acquired by previous editions. Though primarily a work of reference, it is easily read. It gives a good account of the relevant anatomy and physiology; a new chapter has been introduced on neurochemistry; and all information is remarkably up to date—a major achievement in so large a book. The clinical and pathological descriptions are clear and the illustrations well chosen and well reproduced. Though the price is considerable, it represents good value.

THE LANCET

LONDON 10 SEPTEMBER 1960

Penicillinase-resistant Penicillin

A NEW penicillin has been prepared which is active against the usual penicillin-sensitive microorganisms and yet resists staphylococcal penicillinase. This is a major event in chemotherapy. From the information given in the *British Medical Journal* last week and in the three papers appearing in our present issue there is good reason to hope that the new BRL.1241 ('Celbenin', Beecham Research Laboratories) will be a means of controlling the staphylococcal infections which have plagued hospitals throughout the world during the past ten years.

The new penicillin is the most important, so far, of the results of the isolation in 1959 of the penicillin "nucleus", 6-aminopenicillanic acid, by BATCHELOR, DOYLE, NAYLOR, and ROLINSON.[1] Chemically it is sodium 6-(2,6-dimethoxybenzamido) penicillinate monohydrate. In the laboratory it inhibits the growth of coagulase-positive staphylococci in a concentration of about 2–4 μg. per ml.[2] no matter whether these staphylococci are sensitive to penicillins G and V, the penicillins on which we have hitherto relied, or resistant to these penicillins even in concentrations as great as 1000 μg. per ml. With cultures of penicillin-resistant staphylococci, the minimum inhibitory concentration of penicillin G is much influenced by the size of the inoculum of test organisms; but with BRL.1241 the inoculum size has very little significance; which is what would be expected, because the BRL.1241 is not destroyed by staphylococcal penicillinase. Human serum does not diminish the activity of BRL.1241. In laboratory tests staphylococci developed tolerance to BRL.1241 only very slowly and not to a great extent—certainly not to a point where reduction in its clinical usefulness would be likely. Among all the cultures of penicillin-resistant staphylococci that have been tested none has been found with a natural resistance to BRL.1241. There is no cross-resistance between BRL.1241 and chloramphenicol, erythromycin, novobiocin, oleandomycin, streptomycin, or tetracycline. Admittedly, penicillinase extracted from cultures of *Bacillus cereus* slowly inactivates BRL.1241; but this does not lessen this antibiotic's efficacy against all staphylococci. Though it actually promotes the formation of penicillinase by cultures of staphylococci, BRL.1241 is itself unaffected by the enzyme, even after long incubation in conditions which inactivated a solution of 1 mg. of penicillin G in ten minutes. Stability of BRL.1241 to staphylococcal penicillinase was unaffected by pH. In view of the importance of the bactericidal activity of penicillin, it is reassuring to know that BRL.1241 is bactericidal at concentrations only slightly higher than the minimum inhibitory concentrations.

Disadvantages appear to be few. Since it is destroyed by the acid in the stomach, the drug is not effective when given by mouth. It has to be injected intramuscularly at intervals of 4–6 hours in doses of 1·0 g; and to give the six-day course of treatment advised by the manufacturers will at present cost a hospital £19 10*s*. The large dosage is made necessary by the relatively rapid excretion of the BRL.1241 and by its having only about a hundredth of the activity of penicillin G. Its injection seems to cause some pain, but this is of the same order as the pain caused by penicillin G; and there is no evidence of any important difference from other penicillins in its liability to sensitise patients. In 2 of 27 children it caused partial replacement of the coccal salivary flora by coliforms, with fatal bronchopneumonia in one of these.[3] In the same group 2 superficial candida infections appeared but responded to treatment with 'Nystatin'. Nasal staphylococci were not eliminated during parenteral treatment, a point of particular interest in view of the findings of Professor ELEK and Dr. FLEMING on p. 569.

Though chiefly valued for its activity against penicillinase-producing staphylococci, BRL.1241 is active also against many other pyogenic gram-positive cocci including β-hæmolytic streptococci, *Streptococcus viridans*, and the pneumococcus. Among the gram-negative microorganisms, BRL.1241 is moderately active against the meningococcus but inactive against the gram-negative bacilli, even against a strain of *Salmonella typhi* which was relatively sensitive to penicillin G.[2] Disappointingly, this excludes from its range of activity an important group including not only the salmonellas but also the coliforms, the shigellas, *Pseudomonas pyocyanea*, and *Proteus spp.*

The possibilities of the new drug will attract wide attention; and already Professor ELEK and Dr. FLEMING have shown how it may be used to eliminate nasal carriers from among hospital staff. In this connection, however, we must repeat that no drug or combination of drugs is ever likely to make hospitals safe for patients unless it is used in a far more responsible and intelligent manner than has been usual since antibiotics became generally available. Furthermore, aseptic methods will have to be better understood and more faithfully practised. Antiseptics will have to be intelligently worked into the gaps which are inevitable in any attempt —however well designed and however scrupulously applied—to make asepsis a method as distinct from an imperfectly understood and often futile ritual. Those best acquainted with bacteria are highly impressed by their powers of survival and adaptability; and if we think we can control them simply by an uncritical and extravagant use of drugs we are likely to do no more than write another chapter in the literature of the bacterial ecology of hospitals. It is vain to hope that indiscriminate chemotherapy will save doctors, or nurses, or

1. Batchelor, F. R., Doyle, F. P., Naylor, J. H. C., Rolinson, G. N. *Nature, Lond.* 1959, **183**, 257; see *Lancet*, 1959, i, 508.
2. Knox, R. *Brit. med. J.* Sept. 3, 1960, p. 690.
3. Stewart, G. T., Nixon, H. H., Coles, H. M. T. *ibid.* p. 703.

administrators from the need to understand the basis and essentials of bacteriology and to plan their acts accordingly. A rational chemotherapy, on the other hand—one that depends on a sensible clinical judgment supported by the best help that the laboratory can give—has indeed an essential part to play in controlling hospital infection. BRL.1241 offers a hope of controlling the staphylococcus, the organism which has been our chief menace in the postwar years. For that we may well be grateful. We should see to it that we use BRL.1241 in such a way that we do not simply substitute gram-negative bacilli for gram-positive cocci and allow the plague to rage as before.

Kidney Homotransplants in Man

SOME of the limitations and potentialities of tissue transplantation are illustrated by two successful attempts at human kidney transplantation. In an article on an earlier page of this issue Dr. DOSSETOR and his colleagues in Montreal report successful homotransplantation between identical twins. The patient, with bilateral chronic pyelonephritis, was grafted with a healthy kidney from her twin sister, and has eventually regained normal kidney function and (after subsequent removal of her own diseased kidneys) normal blood-pressure—both maintained now for more than a year. This achievement follows a series of similar operations in Boston by MERRILL and his fellow-workers, who reported their first success in 1956.[1] In such operations, involving identical twins, the homotransplant is in effect an autotransplant, and the problem is one of surgical method (here the preliminary animal work of DEMPSTER and his associates [2] is pre-eminent) and of management. This approach is gaining acceptance as a possible means of countering severe bilateral kidney disease in the rather rare event of the existence of an identical twin.

The identity of twins is probably best determined (as it was in DOSSETOR's case) by exchange of skin grafts. Uniovular twins, genetically and therefore antigenically identical, accept each other's living tissues as their own; and a successful exchange of grafts, by proving identity, excludes a major biological hazard of transplantation—the homograft reaction. The rejection of skin grafts between individuals who are not identical twins is a familiar example of the homograft reaction, which, as we now know from the work of MEDAWAR [3] and his group, is essentially an immunological effect. The host, recognising the donor graft tissue as antigenically different from his own, mobilises a cellular reaction leading to necrosis and rejection of the graft. That a second graft from the same donor is rejected at a characteristically accelerated rate suggests that the reaction has an immunological basis, and this has been amply confirmed experimentally. It is the more remarkable, therefore, that MERRILL and his co-workers [4] now report a case of chronic glomerulonephritis with uræmia in which they successfully transplanted a kidney from a twin brother whose non-identity was demonstrated by his rejecting a skin graft from the patient. An unusually close antigenic relationship was nevertheless indicated by the slowness with which the healthy twin rejected the first skin graft (a second graft was rejected rapidly) and by consanguinity in no less than 25 blood-groups tested. The patient himself did not reject his twin's skin graft; but this was not considered evidence of identity, since skin homografts are known to survive exceptionally long in uræmic patients. In these somewhat unusual circumstances MERRILL and his colleagues applied whole-body irradiation in low dosage (without marrow infusion) in the hope of averting the immediate antibody response that would otherwise be engendered by transplanting the healthy kidney. This operation was then successfully carried out and a functioning kidney established. A week later, when irradiation had reduced the white-blood-cell count to less than 50 per c.mm., the patient's critical condition prompted surgical exploration, which revealed an acute abscess involving the patient's own right kidney. This was drained and both his kidneys were removed. The spleen only was irradiated after the operation; and within a few weeks the patient's condition improved greatly: his white-blood-cell count rose, and his blood-pressure, heart size, and kidney function returned towards normal. Ten weeks after operation he was discharged from hospital, and he has remained symptom-free and active for more than a year. Six months after its implantation the skin graft he had received showed slight atrophic changes, suggesting that it was undergoing very slow rejection. Biopsy of the transplanted kidney showed cellular changes with the same implication, despite good kidney function. This situation was met by repeated low-dose irradiation of the whole body, and by large doses of steroids—a combination which probably prevented a fatal homograft reaction.

Experimentally, immunological unresponsiveness to living tissues from another member of the same species can be induced fairly easily in embryonic or newborn animals by introducing living donor cells. According to BURNET's [5] concept, developing cells that are immunologically competent may be killed by such continued exposure to antigens against which their specificity is directed; and mature immunologically active cells may be killed by irradiation or by cytotoxic drugs. MERRILL and his colleagues suggest that in their case the effects of low-dosage irradiation in reducing the number of mature antibody-forming cells able to respond to the foreign stimulus, and the check to proliferation of immature cells imposed by the implantation of such a plentiful source of antigen as a kidney, together favoured graft survival. A similar partial tolerance has been observed by BEILBY et al.[6] in a patient in whom

1. Merrill, J. P., Murray, J. E., Harrison, J. H., Guild, W. R. *J. Amer. med. Ass.* 1956, **160**, 277.
2. Dempster, W. J. *Brit. J. Surg.* 1953, **40**, 447. Dempster, W. J., Jockes, A. M., Oeconomos, N. *Ann. R. Coll. Surg. Engl.* 1955, **16**, 324.
3. Medawar, P. B. *Proc. roy. Soc.* B. 1956, **146**, 1.
4. Merrill, J. P., Murray, J. E., Harrison, J. H., Friedman, E. A., Dealy, J. B., Dammin, G. J. *New. Engl. J. Med.* 1960, **262**, 1251.
5. Burnet, M. The Clonal Selection Theory of Acquired Immunity. London, 1959.
6. Beilby, J. O. W., Cade, I. S., Jelliffe, A. M., Parkin, D. M. *Brit. med. J.* 1960, i, 96.

agranulocytosis developed during treatment with the cytotoxic drug, chlorambucil. A marrow graft from her sister survived, and produced the blood-picture of a red-blood-cell chimæra which persisted for at least nine months, although a skin graft from the same donor was not tolerated. The success of implantation depends also on absence of reaction by the graft against the host. This—the reverse side of the coin—is well known experimentally with both kidney and marrow, and the apparent absence of such a reaction in these two cases may be associated with a chance distribution of antigens between host and graft favouring survival.

Supersonic and Hypersonic

AVIATION medicine is entering a new phase. This much was made clear by the fifth European Congress of Aviation Medicine, held in London on Aug. 29 to Sept. 2, and attended by delegates not only from Europe but also from the Commonwealth and the United States. The theme of the congress—"the medical problems of supersonic and hypersonic flight"—with its play on Latin and Greek prefixes, introduced a flavour of duality. "Supersonic", as one of the chairmen pointed out, is reserved for speeds up to five times the speed of sound, beyond which "super" gives way to "hyper". Broadly speaking, the adjective "supersonic" invites the noun "aircraft"; "hypersonic" is an unfamiliar word which suggests association with missiles and flight outside the atmosphere. There are signs that aviation medicine is about to divide into one branch concerned with the subsonic and supersonic, and a second, almost entirely military, branch concerned with hypersonic flight and hence with space travel.

Since the 1914–18 war the air forces have taken the leading part in aviation medicine research, meeting and solving the difficulties of adapting the man to the aircraft and the aircraft to the man years before similar problems arose in civil practice. The civil agencies have wisely been content to draw on military knowledge and experience, with minor modifications of equipment and procedure. Each major advance in aviation has been well proved in military service before it was adopted for civil use, the sole and tragic exception being the early Comet. This convenient arrangement may now be at an end. The airlines and the manufacturers of civil aircraft are turning their attention to the production of supersonic aircraft which, flying at three times the speed of sound (Mach 3), will reach New York $2^1/_2$ hours after leaving London. If the normal evolutionary process were to continue, we should expect to see such an aircraft in operation about five years after a supersonic military transport had been proved by the air force; but the first Sputnik and the subsequent remarkable advances in rocket technology have introduced a sharp peak into the curve of progress. Though supersonic aircraft have been in military service for some time, they have all been relatively small, carrying a crew of no more than two or three; at the time when large supersonic bombers should have begun to appear in prototype, the rocket made them militarily obsolete and they were abandoned. Thus the air force interest passed abruptly from small supersonic aircraft to hypersonic vehicles, and the manifold problems which a large supersonic transport will present are likely to take second place to the fascinating challenge of space flight. This may mean that civil aviation will have to stand on its own feet, undertake its own research, and solve its own problems. No doubt the civil doctors can count on support from their military colleagues, but this help may be a diversion from the main military effort and on a research basis rather than the sharing of doctrine already established by experiment and validated by practical operating experience. Whether the expansion of civil aviation medicine research will come from manufacturers, airlines, or civil additions to the military institutes remains to be seen. The American Federal Aviation Agency has formed a Civil Aeromedical Research Institute which, though at present undertaking modest investigations into the methods of selecting air-traffic controllers, may perhaps later turn to the more ambitious problems of the supersonic passenger aircraft.

Many of these problems were discussed at the congress. There have been differences of opinion, even among those in the counsels of the aircraft manufacturers and the air corporations. For example, Mr. C. S. R. MARSHALL, of Hawker Siddeley Aviation, feels that a supersonic airliner should have no windows, for the sound technical reason that transparencies do not take kindly to great changes of temperature, and any weakness in the walls of a cabin which will travel at Mach 3 at 70,000 feet is out of the question. Mr. P. G. MASEFIELD, president of the Royal Aeronautical Society and a prominent figure in both airline management and aircraft manufacture, says it must have windows, for the sound commercial reason that passengers like to feel they can look out even when there is nothing to see. There was no dissent, however, when Mr. MASEFIELD, in discussing whether the new airliner should fly at twice or three times the speed of sound, gave as a reason for preferring the latter that no seat in the world really fitted the human posterior for more than two and a half hours.

Those who live near airports are already martyrs to the noise which seems inseparable from flying. The supersonic airliner is not likely to bring any relief in these areas, but it may make the rest of us a good deal more sympathetic. Unless the aircraft stays below the speed of sound until it is near the top of its initial climb, a loud and continuous sonic boom will sweep the countryside over which it flies. It is perhaps as well that most of the flight path is likely to be over the sea. Inside the cabin, the noise level will be very high unless exceptional measures are taken to insulate the walls.

However well an aircraft is designed and built, it is only as safe as the men who fly it. Dr. E. C. POULTON reminded the congress that there is a measurable mental load in keeping oneself prepared for something to happen during the performance of a routine task, and this may increase reaction-time by as much as 40%. The pilot of a jet aircraft, while attending to the routine conduct of the flight, is continuously alert for the unex-

pected, which in such aircraft may manifest itself with great suddenness. By reacting immediately he can usually prevent an incident from becoming an emergency, or an emergency from becoming a disaster. It is, therefore, of the greatest importance to lighten the work load on the crew as much as possible and to make all their equipment thoroughly reliable. What applies to the aircrew applies also to the air traffic controllers, whose job is highly responsible and exacting.

It is to be hoped that certain subjects not mentioned at the congress are still in the minds of the delegates—especially those who have the ear of the airline presidents. There is no reason to suppose that supersonic airliners will be entirely free from accidents, minor if not major. Despite the care which will be lavished on automatic control systems, unbreakable cabins, ozone filters, and other elaborate devices, there is still a place for simple life-saving measures. The backward-facing seat,[1] properly stressed and anchored to the floor, has saved many lives in subsonic aircraft and will save many more. Even supersonic aircraft land at subsonic speeds; and it is just as great a tragedy for a passenger to die an avoidable death at 100 knots as it is to die an unavoidable death at Mach 3.

Food and Population

THE principal subject discussed at the meeting of the British Association in Cardiff this week was food-supplies for a world population which is increasing much faster than had been foreseen. Since the swelling millions are in part the product of successful preventive medicine, our profession has no small interest in the matter; and it is evidence that our ethos is generally accepted that no speaker even hinted that we should do better if we ceased our attempts to eradicate malaria and such scourges. Nobody, in fact, gave more than a passing glance to the possibility that human increase might be checked, as it was for so many centuries, by war or by some fresh plague arising from bacterial or viral mutation.

At the moment there is just enough food to serve its purpose. Very many people suffer from a shortage of food or a shortage of the right food; but if methods of preservation, transport, and trading were perfected there would be enough for the world population of about 2500 million. A reasonable forecast, however, raises this figure to 6000 at the end of the century; and the increase will not be uniform. The population of Africa may have multiplied 2·5 times and of Latin America 3·5 times: indeed the increase is likely to be most in those continents where the agriculture is least efficient. First thoughts suggest that it would be easier to decrease fertility than to increase food production at this rate, but the effects of lowered fertility can be overestimated. Were the fertility of the people of India halved there would still be 200 million extra mouths to feed in 1986. Nevertheless the dangers of starvation are so real that search for a method of birth control equally suitable for illiterate peoples is an urgent necessity. Some Japanese field trials now in progress could have valuable results.

Increasing the world's supply of food is a far more complex problem. Seven-tenths of our globe is either too cold, too dry, or too hilly for farming. Some countries use almost all their available land: some use less than half of it. Between different countries the actual productivity of what is used may vary by a factor of 20. The potential productivity can usually be judged only where farming has already reached a high standard: production in England and Wales could be raised 50% if we wished. As Sir ALEXANDER FLECK pointed out, one of the simplest factors limiting yields is the supply of nitrogen. The Japanese use 100 lb. per acre, with as much dung as they can collect, on their paddy fields and obtain 35 cwt. of rice. The Indians use 1 lb. per acre, burn their cow dung for fuel, and obtain about a quarter of this yield. (One plan for improving Indian farming is the planting of forests, which will provide wood for fuel to replace the cow dung which would do more good on the land.) Asia uses about 2 million tons of nitrogen a year: 7 million might have an immediate effect in raising the level of subsistence. Nitrogen, however, cannot be charmed from the air by the wave of a wand. To fix 1 ton of nitrogen demands 4 tons of coal or 17,000 kilowatts of electricity. India has already begun to develop hydroelectric power on the grand scale and has brown coal in abundance. The prospects of atomic power are promising. In many places natural gas is allowed to burn to waste.

In the West our emphasis is now upon output per man: in the East it must be upon greater output per acre. In a country where a pair of hands is one of the cheapest commodities, labour-saving machinery can produce untoward results. Tractors have prestige value, as the Russians taught us; but a more efficient plough to be drawn by bullocks might do more to help the Indian farmer. Many of the underdeveloped lands are either too wet or too dry, and water is shifted by methods which seem to have been unchanged since time began. A small, efficient, and foolproof electric pump sold cheaply might make great changes. Bulldozers may be needed to clear forest and heavy tractors to break hard pans, but the designing and making of effective tools for peasant farmers is one important way in which the West could help.

At scientific gatherings it is assumed that all evils will yield to the magic word "research": equally, that the process will take some time. Research on food production is certainly far more urgent than the fashionable junketings with space travel, but Prof. H. D. KAY must have startled some of his audience by his dictum that our present knowledge is enough to raise yields by over 50% in most parts of the world. It has been done here and there. A fifth of the money now spent by many indigent countries on weapons of war would buy enough improved seed, fertilisers, and barbed wire to make a sound start. Research there must be; but the problem is too urgent for waiting.

The next step must surely lie with the responsible

1. See *Lancet*, 1959, i, 1275.

Governments. Not all of them have yet appreciated the consequences of a lower death-rate. Some support social structures which make agricultural improvement almost impossible. It must be made clear that this is a problem which affects every man, woman, and child alive and all those to be born. Those countries which now enjoy easier circumstances can help in many ways. There are difficulties in making full use of agricultural surpluses, but it is shameful that in one country malnutrition should be a problem and in another not 200 miles away obesity causes more trouble. The richer countries provide advice freely and generously through F.A.O. and W.H.O. They can provide far more: more trained staff, more machinery, more money, and more stable markets. They must do more than they do in training as agriculturists, engineers, and economists those who are willing to become citizens of the world. When they have done their best it is unlikely that it will be enough. They must expect no returns and no gratitude, because when the larder is empty we shall all suffer one way or another.

Those who founded the British Association would have found this discussion profoundly interesting and probably quite unbelievable. MALTHUS had been dead ten years or so, and the advances of science about which they had been hearing made his gloomy forecasts ridiculous. We wish they were.

Annotations

RADIOGRAPHY IN COMPRESSED-AIR ILLNESS

A RECENT study [1] of decompression sickness during the construction of the Dartford Tunnel is of special interest because of the radiological investigations, the first to be made during a compressed-air undertaking. By their painstaking inquiries, Campbell Golding and his colleagues have provided information which may help to prevent the serious forms of decompression sickness, which are still more common than they should be.

A number of Dartford workers had signs of involvement of the central nervous system. After one man had been treated successfully in May, 1957, a chest X-ray revealed air cysts in the right lower lobe. Although there was at that time no other evidence of an association between decompression sickness and lung disease, the peculiarities of the case pointed strongly to such an association. Radiographs of the chest were therefore taken systematically thereafter, and, in February, 1958, a man similarly affected was found also to have a cyst, with a fluid level in it. These observations raise the neglected question of the significance of pulmonary changes in decompression sickness. Case and Haldane [2] described a pneumothorax developing as a result of exposure to high pressure and subsequent decompression, and they suggested that a cyst or bulla in the lung ruptured. A more closely related observation was made by Liebow et al.[3] in two men who had air-embolism during training for submarine escape, in which rapid ascents were made in water. In one fatal case a broncholith, with air trapped beyond it, was found post mortem; and in the other man a large lung cyst was demonstrated radiologically, which after successful treatment of the air-embolism disappeared.

There has been, of course, much work on burst lung, in which the lung parenchyma tears when the intrapulmonary pressure rises. But the possibility that a localised air sac may, during decompression, discharge bubbles into the pulmonary veins, without other gross damage, is an important one, for it implies that conditions such as bronchitis or emphysema, in which there might be local air trapping, could lead to air-embolism. Disease of the lungs, it has been thought, might hinder exchange of nitrogen between the blood and the alveolar spaces and so aggravate decompression sickness; but the danger of emboli, not from supersaturation of the tissues with dissolved nitrogen but from decompression of trapped air, has not previously been considered and needs to be examined in detail.

The Dartford investigators also began a radiographic survey of caisson disease of bone, which is at present best understood in its later (and irretrievably disabling) stages. Of 80 men who had had sickness in the form of " bends ", but with no permanent after-effects, 10% showed evidence of aseptic necrosis of bones. Most lesions in this series were relatively slight, often difficult to detect, and with only a slight resemblance to the advanced disease recorded in the literature. Similar minor lesions were also found in 3 out of 20 men who had never had an attack of " bends ", although they had had the minor pains which are called " the niggles " and often ignored among compressed-air workers. It is known that this necrosis is not accompanied by symptoms unless the articular surface is involved, and the lesions described are presumably at the earliest (and perhaps still reversible) stages of the disease.

It is often difficult to take X-rays on the site of a compressed-air working, but the possibility of detecting and excluding men liable to air-embolism of pulmonary origin or to necrosis of bone makes it essential that this work be continued and extended. A man who died recently after decompression is reported to have had a lung cyst, and his death may therefore have been preventable. When large numbers of men are working in compressed air, it would contribute notably to their welfare (and probably to our knowledge of this condition) to provide an X-ray unit and a full-time doctor on the site, as was done at Dartford.

1. Campbell Golding, F., Griffiths, P., Hempleman, H. V., Paton, W. D. M., Walder, D. N. *Brit. J. industr. Med.* 1960, **17**, 167.
2. Case, E. M., Haldane, J. B. S. *J. Hyg., Camb.* 1941, **41**, 225.
3. Liebow, A. A., Stark, J. E., Vogel, J., Schaffer, K. E. *U.S. Armed Forces Med. J.* 1959, **10**, 265.

DECIMAL DOSAGE

THE proposed replacement of the apothecaries system by the metric to express the strength of tablets, capsules, and injections in the 1963 edition of the *British Pharmacopœia*,[1] is a major step towards the eventual abandonment of the apothecaries system. That this is a desirable aim is now beyond dispute; the General Medical Council, the British Pharmacopœia Commission, and the Pharmaceutical Society are committed to this end; but the mechanics and timing of the final step are highly controversial. This week at the British Pharmaceutical Conference in Newcastle upon Tyne, Dr. K. R. Capper [2] pointed out that we are at the half-way stage in the use of the two systems. We still expect a dose of scopolamine to be expressed as a fraction of a grain, but we accept

1. British Pharmacopœia Commission: statement on abandonment of the apothecaries system, September, 1960.
2. Capper, K. R. *Pharm. J.* (in the press).

pethidine in terms of milligrammes; in an injection containing a mixture of the two drugs the manufacturers tactfully label the ampoules in both systems.

In the abandonment of the apothecaries system some of the more complex problems envisaged by Capper concern liquid medicines for internal use: a new range of containers would be required; agreement would have to be reached on the capacities of the containers and on the appropriate dose-volumes; legislation would be required to enable a pharmacist to supply the metric equivalent quantity, which might differ by as much as 8% from the amount ordered in the apothecaries system; and the public would need a new range of domestic measures for medicines and to be trained in their use. Capper suggests that the apothecaries system should be abandoned in three stages: first, tablets, capsules, and injections; secondly, liquid medicines for external use; leaving liquid medicines for internal use as the final stage. This he believes could be introduced by September, 1973.

How long the apothecaries system survives may depend less on the timing of official pronouncements than on whether aids to its survival are provided—for example, the proposed pharmacopœial table of equivalent quantities, where there is a variation of from 60 to 66·66 mg. to the grain to allow particular fractions of a grain to be converted to a metric equivalent in good round numbers. The humble gr. 5 aspirin tablet will settle the issue in 1963. If the new *B.P.* requires an aspirin tablet to contain a "metric equivalent quantity" of 300 mg. (dose: one to three tablets) the apothecaries system will survive; if the truly metric quantity of 250 mg. (dose one to four tablets) is required, the end of the apothecaries system will be in sight.

PROGNOSIS OF SUBARACHNOID HÆMORRHAGE

A FURTHER study of the prognosis of subarachnoid hæmorrhage has lately been published. Pollack and Paddison [1] report a series of 134 cases admitted to the Charity Hospital of New Orleans in the years 1950–56. They applied the recognised diagnostic criteria, excluding all those elderly hypertensives in whom the presence of a primary intracerebral hæmorrhage was presumed, as well as traumatic and neonatal cases. The series comprised 82 women and 52 men: 57 patients died—an overall mortality of 43%. Of the 57 deaths, 38 occurred in the first week after the ictus, and half of these within the first twenty-four hours. The outcome of the illness was apparently uninfluenced by sex but was considerably worse if the patient was comatose or semi-comatose and if he was elderly or hypertensive. Bleeding recurred in 19 cases; and 13 of these patients died. Carotid arteriography was performed in 62 cases, and aneurysms were demonstrated in 33 of these; in another 10 cases aneurysms were demonstrated subsequently at necropsy. Hence a total of 44 cases had proven aneurysms, and in this group the mortality-rate was 41%—a figure similar to that for the entire series. In 28 of these cases, however, surgical treatment was carried out; a total of 11 patients in the surgical series died, and in these individuals too the outcome was influenced adversely by the presence of hypertension.

It is now widely agreed that about 45% of patients with spontaneous subarachnoid hæmorrhage die; many do so within the first twenty-four hours, many more from recurrent bleeding in the first four weeks after the ictus. Increasing age, coma, hypertension, and neurological signs indicating intracerebral hæmorrhage or coexisting infarction all influence the outcome adversely.[2 3] With bilateral carotid arteriography many workers have, like Pollack and Paddison, failed to demonstrate aneurysms in much more than half the cases. This is partly because vertebral arteriography is not routinely performed, but it may be due also to imperfect radiological technique. Perrett and Bull [4] have described a series of 210 cases of proven intracranial aneurysm in 89% of which the aneurysm was demonstrated angiographically; they give reasons for supposing that the potential accuracy of the method is about 96%. Furthermore the terms "subarachnoid hæmorrhage" and "ruptured intracranial aneurysm" are applied to subarachnoid bleeding due to angiomas and other lesions; and the prognosis and results of treatment can properly be compared only in series in which the cause of the bleeding is known. Nevertheless, in the series described by Pollack and Paddison, the accuracy of radiological diagnosis may have been below the ideal; 28 selected cases were subjected to surgical treatment and were yet taken into account when the prognosis of all cases was considered; and the surgically treated cases were subjected to many different operations at different intervals after the hæmorrhage. In other words, the findings of this particular study do not help in deciding on the relative merits of conservative and of surgical treatment. These remarks are not intended as criticism of the authors' approach; for they reported the facts concerning the recognised methods of investigation and treatment of such cases in their hospital, and there are few hospitals anywhere in the world in which the management of subarachnoid hæmorrhage is any better organised.

McKissock et al.[5] have published the first results of a carefully controlled trial of treatment. In a consecutive series of cases of subarachnoid hæmorrhage, patients in whom surgically accessible aneurysms were demonstrated by arteriography were considered for inclusion in the trial according to a series of strict diagnostic criteria. A random selection was then made from cases regarded as suitable for surgical treatment, in such a way that half were subjected to operation and half were treated conservatively. Much evidence has recently accumulated to suggest that the difficulties and complications of surgical treatment may depend largely on the situation of the causal aneurysm; for this reason the results for aneurysms in different situations are being analysed separately, and in their initial report McKissock et al. describe their results in 94 patients with aneurysms of the internal carotid artery situated at or near the point of origin of the posterior communicating artery. 11 patients, who were so ill on admission that they seemed likely to die forthwith, were not benefited by surgical treatment. Of the remaining 83 patients, 42 were treated conservatively and 15 (35%) died. In the other 41 cases which were treated surgically (usually by carotid ligation) there were only 4 deaths (10%). These figures clearly indicate that patients with subarachnoid hæmorrhage arising from an aneurysm in this particular situation who survive the first few days can be benefited by surgical treatment. The results in patients with aneurysms in other situations are eagerly awaited. Meanwhile, studies such as that of Pollack and Paddison remind us that subarachnoid hæmorrhage is a serious condition with a high mortality. Clearly a planned routine of investigation and management in specialised centres is indicated.

1. Pollack, S. L., Paddison, R. M. *Ann. intern. Med.* 1960, **52**, 1088.
2. Walton, J. N. Subarachnoid Hæmorrhage. Edinburgh, 1956.
3. McKissock, W., Paine, K. W. E. *Brain*, 1959, **82**, 356.
4. Perrett, L. V., Bull, J. W. D. *Brit. J. Radiol.* 1959, **32**, 85.
5. McKissock, W., Richardson, A., Walsh, L. *Lancet*, 1960, **i**, 1203.

EXFOLIATIVE CYTOLOGY IN PERNICIOUS ANÆMIA

THE earliest cytological observations in pernicious anæmia (P.A.) were, of course, those relating to red blood-cells. Besides commenting on changes in mature red cells, Ehrlich [1] applied the term megaloblast to large nucleated precursors present in peripheral blood. Abnormal features were later noticed in cells of the myeloid series. Many clinical characteristics of P.A., including lingual and gastric atrophy, premature greying of hair, and degeneration of the spinal cord, indicated that this is a general, and not a strictly hæmatological, disease. From study of cells exfoliated from various epithelial surfaces, it is becoming clear that cytological abnormalities are widespread and common.

Rubin and Massey [2] observed enlargement of nuclei of gastric mucosal cells obtained by gastric washings in patients with P.A. who had already received treatment. Graham and Rheault [3] described enlargement of both nucleus and cytoplasm of squamous epithelial cells that had been shed from mouth or œsophagus in patients with P.A. in relapse. A high prevalence of multiple nuclei was also noted in exfoliated squames from these patients. The nuclear abnormalities of squamous cells in P.A. were confirmed by Rubin [4 5] and Massey and Klayman,[6] who suggested that these occurred in other megaloblastic anæmias. In gastric washings on patients with P.A. some of the gastric epithelial cells were found to be abnormal, having either a "bland" nucleus or an "active" appearance, with clumping of chromatin and prominent nucleoli. Rubin [4] remarked, however, that "active" cells may be found in washings from patients with simple achlorhydria without P.A. Such cells do not necessarily disappear with treatment; and Henning and Witte [7] and Schade [8] emphasise that they are not pathognomonic of P.A.

Boddington and Spriggs [9] studied cells from nasal mucosa, urinary tract, and vaginal and gastric epithelial surfaces. They concluded that widespread epithelial-cell changes might take place in P.A. and that these were reversed by treatment, but that the appearances were too inconstant and non-specific to have much diagnostic value. Squamous cells from buccal mucous membrane are the most easy to examine; and, by measuring nuclei, Boen [10] and Farrant [11 12] have confirmed that abnormalities of shape and size occur in P.A. Boen et al.[13] described a patient with neurological changes of subacute combined degeneration of the cord, in whom the hæmoglobin level and marrow were normal. The serum-vitamin-B_{12} level was reduced, and the buccal epithelium showed nuclear pleomorphism and giant nuclei, which reverted to normal after a week's treatment with vitamin B_{12}. Boddington and Spriggs [9] refer to a case in which the epithelial changes strongly suggested deficiency of vitamin B_{12}; an initial marrow examination was not diagnostic, but the diagnosis of P.A. was confirmed by a second marrow aspiration.

Clearly the cytological examination of buccal epithelium is only occasionally of diagnostic value in cases of suspected vitamin-B_{12} deficiency. But it does seem that vitamin B_{12} may be necessary for the normal maturation of many cells besides red and white cells, and that it may be an essential factor for normal nuclear metabolism. Mallarmé [14] viewed P.A. as a nutritional cytological dystrophy, and the latest evidence supports this view.

1. Ehrlich, P. *Berl. klin. Wschr.* 1880, **17**, 405.
2. Rubin, C. E., Massey, B. E. *J. Lab. clin. Med.* 1953, **42**, 942.
3. Graham, R. M., Rheault, M. H. *ibid.* 1954, **43**, 235.
4. Rubin, C. E. *Gastroenterology*, 1955, **29**, 563.
5. Rubin, C. E. *Ann. N.Y. Acad. Sci.* 1956, **63**, 1377.
6. Massey, B. W., Klayman, M. I. *Amer. J. med. Sci.* 1955, **230**, 506.
7. Henning, N., Witte, S. Atlas der Gastroenterologischen Cytodiagnostik. Stuttgart, 1957.
8. Schade, R. O. K. Gastric Cytology. London, 1960.
9. Boddington, M. M., Spriggs, A. I. *J. clin. Path.* 1959, **12**, 228.
10. Boen, S. T. *Acta med. scand.* 1957, **159**, 425.
11. Farrant, P. C. *Lancet*, 1958, i, 830.
12. Farrant, P. C. *Brit. med. J.* 1960, i, 1694.
13. Boen, S. T., Molhuysen, J. A., Steenbergen, J. *Lancet*, 1958, ii, 294.

TOXOCARAL PSEUDOGLIOMA OF THE RETINA

THE differential diagnosis of glioma of the retina presents two problems: it must be distinguished, first, from non-malignant conditions, and secondly from the different types of pseudogliomatous reactions which themselves are not easily recognised. Both these difficulties are well shown by a study of 53 cases in children up to 5 years of age in whom an eye was enucleated on the suspicion of retinoblastoma.[15] The diagnosis was found correct on histological examination in 24 cases; but in the remaining 29 cases a mass of inflammatory reactions and congenital anomalies—some fairly well defined, others ill understood—were found. In this series, from two Central European centres—Rostock and Magdeburg—no retrolental fibroplasia was observed.

In 1950 Helen Wilder [16] drew attention to the presence of nematode larvæ in a series of pseudogliomas studied histologically. The unexpectedly high rate of such findings raised the question whether her material was representative; but Wilder herself held that nematodes were an important cause of blindness in American children. Six years later Nichols [17] re-examined five of the cases in Wilder's series and identified the nematode as the second-stage larvæ of *Toxocara canis*. This established for the first time that the dogworm could infect the human eye. Confirmation came, in 1959, from Irvine and Irvine,[18] who observed *T. canis* in an eye which had been diagnosed clinically as the seat of retinoblastoma. Further support now comes from a study of four cases by Ashton.[19] These were obtained from the material at the Institute of Ophthalmology in London and concerned children who had had an eye excised on the suspicion of tumour. The children hailed from London, Bristol, Taunton, and Kilmarnock, and were aged 8, 16, 11, and 4 years respectively. The diagnosis in each case had been difficult and uncertain both clinically and histologically. Re-examination of these eyes now reveals that they are affected by solitary retinal masses caused by toxocara, histologically demonstrable.

Toxocara is as widely prevalent in dogs in this country as elsewhere, and the recognition that ocular toxocara infection does occur in this country raises the question of the frequency and manifestations of this infection here as a general disorder as well as an ocular disturbance. Diagnosis is still difficult, and for the present the one laboratory finding that may reinforce the tentative diagnosis of ocular toxocara infection is a high eosinophil-count.

Sir WILFRID LE GROS CLARK has been elected president of the British Association for the Advancement of Science for 1961.

THE death is reported from Metz of Dr. MARJORY WARREN, physician to the geriatric unit of the West Middlesex Hospital, from injuries received in a road accident.

14. Mallarmé, J. *Blood*, 1948, **3**, 103.
15. Heydenreich, A. *Klin. Mbl. Augenheilk.* 1959, **134**, 465.
16. Wilder, H. C. *Trans. Amer. Acad. Ophthal. Otolaryng.* 1950, **55**, 99.
17. Nichols, R. L. *J. Parasit.* 1956, **42**, 349.
18. Irvine, W. C., Irvine, A. R. *Amer. J. Ophthal.* 1959, **47**, 185.
19. Ashton, N. *Brit. J. Ophthal.* 1960, **44**, 129.

Special Articles

METAMORPHOSIS OF A MENTAL HOSPITAL

Application of McKeown's Comprehensive Unit

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THE idea of a comprehensive hospital is not new. It has been considered and mooted for some time. In 1958 it was cogently described by McKeown, who classified patients into four groups:

Group 1: those who need full hospital facilities, such as frequent medical attention and skilled nursing.

Group 2: those who need limited facilities, such as simple nursing, washing, dressing, feeding, bowel and bladder attention, but no mental supervision.

Group 3: as in group 2 but with mental supervision.

Group 4: those who need no special medical or surgical facilities and who remain in hospital chiefly for social reasons.

McKeown's proposals were published at about the same time as we were considering the future policy and planning of this mental hospital of over 2000 beds. Because of the shift of emphasis to outpatient treatment, the more potent treatment of inpatients, and a more-than-averaged-aged patient population our numbers between 1954 and 1959 fell from 2784 to 2143 with the almost unheard-of possibility of wards becoming empty. Early in 1959 the speed of this change was slowed by the addition of another quarter of a million to our catchment population, which doubled overnight our potential patient intake. This slowed but by no means stopped the run-down, because its effects were partly offset by the policy of our regional hospital board of opening psychiatric units attached to general hospitals. Such units, when properly staffed and vigorously used, can reduce admissions to mental hospitals to a very small number.

We thus found ourselves with large buildings, most of which had received a great deal of structural renewal and maintenance, together with elaborate and efficient services of heating, electricity, water, and so on. We had first-class pathological, physiotherapy, surgical (particularly neurosurgical), and neuroradiological facilities and equipment. Even more important were our human resources in the form of the nursing staff, many of whom, especially on the male side, were doubly trained. And a definitely falling patient population.

Had we any doubts about the trend these were removed when we considered the implications of the Mental Health Act. Here was a deliberate and planned intention of a change of emphasis from hospital to community care with funds potentially available to set up hostels for people who could quite well live outside the hospital if accommodation were available.

Faced with these facts we tried to draw up a definite and coherent policy and plan which would make good use of our accommodation, nursing staff, and ancillary services, and at the same time cater for a definite need in the community. This is the nexus of the whole plan. We are catering for needs that have been apparent and known for some time. We are not trying to revive a corpse or shore up, for specious reasons, buildings that ought to come down. Nor indeed are we attempting to make the hospital " play Hamlet after the age of 60 " against the advice of Beerbohm Tree. We believe that, though its function is changing, the major part of the hospital itself will continue to supply a service which will be necessary so long as there are people who need hospital care and attention.

METHOD OF REORGANISATION

An isolated building with about 200 beds hitherto occupied by women patients (many of whom could have been discharged had there been anywhere for them to go) was transformed with little effort into a psychiatric admission unit for about 110 women and 90 men. To this unit all our admissions go at present, except for a few aged men who are admitted to their own detached ward of undesignated beds (90) and a small number of aged women who also have their own undesignated geriatric ward (66).

Our psychiatric admission unit, therefore, caters for the inpatient treatment of patients coming from a population of half a million people. This is less than $^1/_2$ bed per 1000 of the population instead of 3 beds per 1000 population usually asked for in Western Europe. Yet so far our unit has not been overcrowded. Our experience is that it can cope with the catchment population provided that there is a reasonable geriatric service which prevents small numbers of psychiatric beds being blocked by aged people.

The geriatric service we have provided ourselves by reclassifying wards and patients. We now have 300 beds for male geriatric patients and 500 for females, including the two undesignated units already mentioned. If a geriatrician should be appointed for the area, a ready-made series of wards or centre will be available for him.

A more detailed survey of one of our male geriatric units might be of interest.

This is our 90-bedded detached building called Cassidy House. An analysis of its bed occupancy shows the following McKeown groupings:

McKeown group	No. of patients	Types of illness
1	19	Post-thrombotic: arteriosclerosis of different kinds, mostly needing bed treatment
2	36	Senile: arteriosclerotic showing variety of pictures—e.g., parkinsonism, Paget's disease
3	8	As above: plus chronic schizophrenics whose active illness has disappeared. All are institutionalised
4	27	Many have very slight memory impairment. Mostly in unit for social reasons

The unit has its own 2 occupational therapists and is run by 2 charge nurses with 2 deputies and a nursing service from the hospital on demand. The doctor in charge is a local general practitioner on a twenty-four-hour call with his partners. It has none of the gentle-decay type of atmosphere of many purely hostel units, and many of the group-3 and group-4 patients are keen to help those of their brethren who are more incapacitated than themselves. For the past year this unit has never had a bed empty for longer than twenty-four hours.

For so-called chronic and long-stay mental patients we still keep about 430 male and 400 female beds. When reclassifying our patients we estimated that about 15% of the men and 20% of the women were in fact defectives who had been transferred from the Merseyside conurbation during war evacuation from hospitals in that area and whose relatives are now apparently non-existent.

Another pressing need has been beds for chronic physically sick patients. By reclassification and inter-ward

transfers, a large detached building of about 80 beds was cleared for this purpose. It was necessary to install two or three sluices, toilets, and so on, but this was a minor task. So far, 30 chronic physically ill men have been nursed there, most of whom have needed full hospital nursing and medical facilities. It is considered that this unit meets the chronic medical needs of the male population of this area. Occupational therapy is given for as many of these patients as are able to carry it out.

In the Manchester region there was a waiting-list of over 1000 patients for mental-deficiency beds. We have accepted 50 defectives who need complete nursing facilities—so-called " cot-and-chair " defectives who fell into group 1. Three of our male nurses were seconded to a mental-deficiency hospital for a year's training and they are now working under the clinical supervision of a consultant from that hospital.

We hope to set up a blood-transfusion unit in another part of the hospital. Technical requirements have delayed its opening, but it will come into operation some time this year, using a building of sound construction but empty of patients.

Other buildings house tuberculous and gastrointestinal patients. These at present are, or have been, mentally ill, but in these two wards (male and female) separate accommodation supplies clinical and pathological services which could in the future easily and efficiently be used for fresh non-mental cases.

We have tried to make the scheme comprehensive but flexible, and if the number of mentally ill patients in need of hospital accommodation continues to fall, the vacant places might well be used for other real, and sometimes pressing, needs—e.g., postoperative orthopædic patients.

MEDICAL SUPERVISION

Most mental hospitals, especially in the North, are short of doctors. About eighteen months ago it was calculated that each doctor in this hospital, assuming he worked his full sessions, without any holidays or extramural activities such as outpatients, was able to give a patient about 4 hours per annum. In practice, of course, many patients did not receive as much attention, which from any point of view was indefensible.

By reclassifying our patients, and particularly by remembering that old people were old people with a variety of organic disorders and not merely " psychogeriatric ", we were able to introduce this large group to general practitioners who were interested in geriatrics.

Three junior psychiatric posts—almost never filled or filled in a very desultory way—were broken up into clinical-assistant sessions for general practitioners. There are now six of these G.P.s, and each has about 200 geriatric patients under his general supervision for the whole twenty-four hours. He is responsible for their clinical, investigational, and therapeutic care, and has the whole range of the hospital's consultant services at his disposal. (The medical superintendent still has statutory obligations towards many of these old people who have been, at some time or another, considered to be mainly psychiatric problems.)

The introduction of general practitioners has been an unqualified success. To their task of looking after the chronic physically ill, including tuberculosis and gastrointestinal patients and the old people, they bring a practical knowledge and stability rarely found among juniors in large mental hospitals. This move has been one of the best sequels to our reorganisation and it has awakened an entirely new therapeutic hopefulness among the nurses and the patients.

The psychiatric staff (consultants, S.H.M.O.s, and two registrars) freed for the first time from non-psychiatric duties, are able to spend all their time in the outpatient departments, the admission hospital, and/or the long-stay annexes in which most of the difficulties and problems are psychiatric.

Though no-one can be antagonistic towards the concept of the " therapeutic community " or to Bickford's (1955) views on the treatment and nursing of the chronic mentally sick, nevertheless we believe that it is important to avoid adding to the numbers of the long-stay mental patients. We believe simply that this addition is unnecessary if we apply modern treatment methods properly and vigorously, with the help of good outpatient facilities, day hospitals, community care, and the provisions of the Mental Health Act of 1959. Furthermore, as we have tried to show, the most obtrusive problem in this hospital is the institutionalised geriatric patient with little or no evidence of psychiatric illness. He belongs properly to organic or structural medicine.

By returning psychiatrists to the practice of psychiatry, we have not only benefited ourselves (and the psychiatrically ill, especially the neurotic who now feels that his doctor has at last some time to give to him), but we have extended McKeown's concept, so that it might now read *not only should there be one type of hospital, but all doctors should work there whether full-time as consultants or part-time as family doctors.*

Such an arrangement could remove many of the anomalies and difficulties of finding junior staff and produce a vast, almost untapped, reservoir of ability much greater than most hospitals have had for years. It is in fact a proposal for a partial return to " pre-1948 " when many family doctors worked in hospitals.

Our thanks are due to the regional hospital board and the hospital management committee for their wholehearted support. We also wish to thank Mr. H. Carr, F.H.A., hospital secretary, and Mr. W. Lewty, B.SC., the hospital engineer.

The introduction of the scheme has meant an almost cataclysmic upset amongst the patients and nurses. Both have cooperated enthusiastically, and indeed at times insisted on overrunning the programme of events. Without these two groups the scheme would have completely failed.

Last, but not least, our thanks are due to our own colleagues who helped to put the plan into operation effectively and efficiently.

REFERENCES

Bickford, J. A. R. (1955) *Lancet*, ii, 917.
McKeown, T. (1958) *ibid.* i, 701.

". . . Science is not an autonomous realm of knowledge, governed by immutable rules, but is a way of doing intellectual business. If I may be allowed an analogy, it is like the Stock Exchange. The price of a particular share on a particular day is not fixed by any one individual, although it may be greatly influenced by big buyers and sellers. The truth value of a scientific theory, also, is not predetermined by the genius of its discoverer but depends on the price which other scientists will put upon it. In science, as on the Stock Exchange, one is bound to be absolutely fair and honest because the long-term profits of decent trading are greater than the immediate gains of fraud. But honesty will not protect any of us, individually, from errors of judgment; in the long run, the market price is the only fair price. There may perhaps be better social means than the Stock Exchange for maintaining the economic health of the nation; I doubt if there is any better instrument for achieving reliable knowledge of the world than a freely co-operating community of scientists.—JOHN ZIMAN. *Listener*, Aug. 18, 1960, p. 252.

Before Our Time

WRITER, DOCTOR, AND PATIENT

Anton Chekhov was born a hundred years ago into a literary epoch that was dominated by tuberculosis. To his generation of writers tuberculosis was an attitude of mind and a way of living, a stimulant of deep emotions, passions, and inspiration; and it was Providence's favourite disguise, both in fiction and in reality. Shortly before he died Chekhov wrote that he had taken Medicine as his wife and Literature as his mistress; and it might have been a singularly happy *ménage à trois*. But at the age of 23, as a starving and high-minded medical student in Moscow, he was already spitting blood " regularly in the wet season " and he was plagued by recurrent laryngitis.

By then he had written scores of short stories—some of them real medical-student literature, brimming with anatomical detail. Dr. Toporkov, one of his creations in *Late Flowers*, percusses and auscultates at length; he notes dullness on the right and crepitations on the left, and bronchial breathing spreading to both bases. But medical peepshows of this kind are unprophetic of Chekhov's writings as a qualified doctor. To his non-medical contemporaries the contrast between the stark facts of the case-sheet and the complexity of life was irresistible: Turgenev rarely missed a chance to spice his tales with clinical irrelevances, and Tolstoi relished medical jargon. Dr. Chekhov's characters, on the other hand, are merely ill: they suffer pain, weakness, and fever; they lie awake at night and cough torments them by day; and they die hoping.

The poor schoolmaster Sisoiev, for example, feels a trifle weary, but on no account would he miss the banquet that is to be given in his honour. Putting on his spotlessly polished black boots exhausts him so much that he has to rest for a while, and in front of the director's apartment he is seized by a bad bout of coughing. So bad that he flings his stick to the floor and his cap drops off his head. When his host and fellow teachers and the school-inspector himself hurry out of the flat he sits gasping at the top of the stairs, covered in sweat. An unfortunate and undignified contretemps, he meditates, when eventually he gets home. He gazes at his drawn, shadowed face in the mirror. " But I'm making a fuss. In fact, my colour is better than it's been for months. If only the gastric catarrh wouldn't bring on that wretched cough." He decides to spend the summer in the South. If only he could scrape up the necessary money.

It might be an episode from one of the middle-aged Chekhov's letters.

* * *

After qualifying he settled in Szumi near Kharkov, renowned for its health-giving climate. But he could not stick his isolation from the country's literary hubbub for long. He returned to Moscow, wrote several short plays, and became a prolific contributor to newspapers and magazines. His favourite brother died in 1889 from tuberculosis, but within a year, with the calculated recklessness of the tuberculous, he set out on a tour of Far Eastern convict colonies. Even by the heroic standards of 19th-century journalism, this was a nightmare journey. He finished *Sahalin*—for an age of social ferment a strangely uncommitted piece of reporting—but on his return he was coughing up blood every morning and became so weak that he could no longer leave his room. This was the classical picture of the young, consumptive, soulsick writer, suddenly brought face to face with the realisation that his years (or months, or weeks, or days) were numbered. In Moscow's bleak midwinter Chekhov was easily persuaded to seek a new lease of life in Italy. A hectic three-months tour of Lombardy, Florence, Rome, and Naples became his honeymoon with death.

He is the hero of *The Tale of the Unknown Man* who develops pneumonia in Venice. It is an odd, nocturnal illness. The Unknown sits at his desk, resting his head in his arms: a dry, lancinating cough keeps him awake until his feet feel like lead, and his neck and back ache, and perspiration runs down his burning forehead. But the daylight is too precious to waste: the backwater canals and piazzas bubble with excitement and adventure. To outsiders such life appeared effervescent, as death at the end seemed tragic and inconsequent. But outsiders could not be trusted: their judgment had been warped by their regulation ten hours' sleep and their perception blunted by crude physical health. The sick man looked at them with ironic detachment: his own extravagances may have been pointless but they were not futile—neither farce nor grand tragedy but a gentle *commedia lacrymosa*.

After a riotous honeymoon even Chekhov's relation with death mellowed into a middle-aged love-affair. Three years later, now a Government dispensary doctor in Melihovo in the Southern Ukraine, he writes: " I'm pretty fit on the whole. True, I cough rather more than I used to and I get short of breath easily, but my consumption is not galloping away with me yet." And a year later: " I'm much better since I cut down my smoking to a cigar a day. What do I do? Well, I do my rounds and tend myself in between: and, of course, we're all waiting for the cholera." This is the period of his great autumnal plays, which he peoples with men and women who are doomed like himself, but who must not be taken tragically. " We shall go on living," says the plain Sophia when she is left alone with Uncle Vanya, " and when the time comes, we shall die submissively." And amid all the slow decay and quiet nostalgia for the passing of beauty, there is always hope—the promise of spring, a certainty that happiness is just round the corner. To the go-getting world beyond the footlights such happiness ought to seem unreasonable, even ridiculous: but it never does. We sense that these people, as they drift from nowhere to nowhere through unchanging lives, have somewhere, somehow, discovered the secret of real change. The key to that secret is missing from our world, and they may have mislaid it themselves; but from their world it is not altogether lost.

* * *

During the years of remission, tuberculosis vanishes from Chekhov's writings: then suddenly, in 1894, it kills Kovrin, the hero of the *Black Monk*. A few months later, walking through the Ermitage, Chekhov, too, has a hæmorrhage and collapses in front of Titian's *Entombment*. He rallies, but he reaches Moscow too weak to get off the train. And so the physicians at the Ostrumov Clinic take over from the doctor-writer:

> Drawn face. Wasted body. Weight 33 kg.; height 186 cm. Extreme pallor; irregular, thready pulse. Poor chest movements with signs of cavitation at both apices. Sputum teaming with Koch's bacilli.

" My crotchety lungs played me up just when I needed them badly," is the patient's comment a week later, " and my learned friends are pouring gallons of *kumisz* into me and insist that I must change my way of life." Despite the mockery, he was a good patient; and from his letters it is hard to say what he thought of his professional colleagues. On the stage they are a mixed bunch. Lvov is a prig—estimable but harsh, intolerant, and an inverted snob. Dorn is a faded provincial *jeune premier* whose

reasonableness and complacency are at time irritating. Chebotykin, the besotted old army doctor, babbles that he has forgotten everything that he has ever learnt, and we have no reason to disbelieve him. But he is happier in his degradation than Astrov, that intense and intelligent man whom the stench, the dirt, the mud, and the smoke of Russia's country towns have driven to drink. Yet, despite the differences, all four are unmistakably doctors. They do not talk shop or venture beyond an innocuous prescription of valerian drops in their therapy; nor do they rise, by virtue of their profession, above humdrum events. (None of Chekhov's heroes do.) But in their different ways they are dedicated men; and if they have not always lived up to the Hippocratic ideals of their youth, well, who in their circumstances would have lived differently?

* * *

After six months' convalescence on the French Riviera, Chekhov settled under the clear, forgiving sky of the Crimea. From his "warm Siberia" he watched the turbulent birth of Stanislavsky's Moscow Arts Theatre; and he gave it wings with *Seagull*. In 1900 the grateful troupe visited him in Yalta and performed on an improvised stage to an enchanted audience that included the young Maxim Gorki and Ivan Bunin. A few months later Chekhov married their leading lady, Olga Knipper. Despite long separations, illness, and a miscarriage, it was a happy marriage. With Olga and Stanislavsky in mind for the leading roles, Chekhov embarked on the comedy *Cherry Orchard*—"a very funny play, at least in intention". By now writing had become a laborious, protracted task, imposing at times almost intolerable physical effort. But he watched his strength ebbing away with neither more nor less compassion than he had given to the characters he had created. The standard he set them when they appealed for sympathy was the simple standard of honesty. He remained passionately on the side of truth, though not the truth of rousing ideas or sweeping political programmes. His truth came and went on tiptoe; it shone in those wordless moments when people recognised the laws of their own existence and made peace with their tiny destinies.

T. L. DORMANDY

Public Health

Infectious Diseases in England and Wales

Disease	Week ended August			
	6	13	20	27*
Diphtheria	2	2	1	1
Dysentery	448	427	346	296
Encephalitis:				
Infective	2	8	5	1
Postinfectious	2	4	..	4
Food-poisoning	236	230	247	190
Measles, excluding rubella	2545	2544	2060	1613
Meningococcal infection	12	25	23	14
Ophthalmia neonatorum	18	17	22	23
Paratyphoid fever	7	6	5	8
Pneumonia, primary or influenzal	135	130	139	158
Poliomyelitis:				
Paralytic	4	7	3	10
Non-paralytic	10	11	7	9
Puerperal pyrexia	145	181	167	154
Scarlet fever	316	252	208	188
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	351	366	359	381
Meninges and C.N.S	3	8	8	3
Other	42	54	45	53
Typhoid fever	2	3	2	3
Whooping-cough	1193	1386	1308	1467

* Not including late returns.

In England Now

A Running Commentary by Peripatetic Correspondents

I ONCE read an article emphasising the importance of making the patient feel at home in hospital. To make him feel at home in a casualty department is by no means easy. Obviously it is not enough for the nurses to leave curlers in their hair or scatter half-darned socks on the chairs, or for a cat to sleep by the fire. No, familiar surroundings are what is meant; and, with the current crop of H-aerials sprouting thicker than resistant staphs on a culture plate, I've come to the conclusion that the place where the local population will feel most at home is the saloons and boardwalks of the Wild West. Even those dimwits who cannot remember the name of their own G.P. can detail how many bullets Doc Holliday of Dodge City removed from John Wesley Hardin after the gunfight at the O.K. Corral.

Our new Western decor should set the youngest viewer at ease immediately. The casualties will pass the hitching-rail—useful for prams and spare children—kick open the swinging half-doors, and hand in their guns at sheriff's office (records). In the corral (waiting-room) we have thrown out all the magazines and are having faro and blackjack tables. The pharmacy, behind a long mahogany bar, have agreed to hand out all medicines in bottles labelled "Snakebite Oil"; but determining the exact amount of gold dust needed to cover the prescription charge is causing us a little bother.

Of course, as is usual when science takes a forward step, there are a few reactionaries. Matron is being sticky about dressing nurses as dance-hall girls—I think the fishnet stockings and feathers are the trouble. Ambulance control flatly refuse to supply Conestoga wagons to move patients and won't hear of closing down their radios and using smoke-signals. Still, most of the other departments are cooperating well. The anæsthetists have accepted our calling a G.A. "smoking the pipe of peace with Sitting Bull", though they don't really like giving premeds with a bow and arrow. The pathologists don't mind someone coming for hæmoglobin or E.S.R. with "make blood brother to Redhand Nation" written on the form. But the radiographers object to their activities being called "havin' yore tin-type took". It's the registrars who are being really difficult. They feel that "send for the U.S. cavalry" is not the correct way to ask them to see a case. But it's the only logical title. After all, they do come galloping when casualty is hard-pressed, and we are always relieved when they arrive.

* * *

Lately our health department has been surfeited with surveys. The nurses have little heart for this kind of campaign. Their heart is in service, not surveys. In their districts they are guiding, cheering, supporting people. This is their role. That is why they endure the drudgery of public health. Gathering statistics for research—whether obstetrical, pædiatric, sociological, or even epidemiological—is an alien skill. They can do it, very well, but not with that deep satisfaction that the born and bred researcher might feel.

I used to accept with proper self-abasement the strictures of our academicians who pointed to our poor output of scientific papers and research. But isn't it natural that where there is complete fulfilment in personal service there is less urge for formal research? The nurse who knows her district as the G.P. knows his practice does not use questionnaires to tell her which illnesses are prevalent, where the problem families are, who is giving the most help to the aged. Let the researchers harvest their own material. The public-health service can guide their inquiries and help them to interpret their findings.

I don't mean that surveys are not in the direct Florence Nightingale tradition. But you can see the difference between a lamp and a questionnaire.

* * *

Many visitors to Paris suffer a certain unease of the intestines, a kind of potential gripes which lies in wait for the least excess of any sort. If you visit a three-star restaurant, you will trigger off a dreadful Nemesis—though you may never know

whether the factor responsible is the richness of the food or the emotional impact of the *addition*. If you smoke too much or if you refrain too strictly from smoking; if you are too busy or too idle; if, in fact, you do anything to disturb the anxious homœostasis of the bowel, however indirectly, retribution will descend. It is a gastrointestinal purgatory; all that may be done is to regulate one's life in such a way that one may eventually pass through it to a higher state of being.

It is some relief to know that this drastic introduction to the Middle Way is not confined to Anglo-Saxon visitors. Parisians themselves know it well and many features of Paris life are unobtrusively geared to meet the challenge. Parisians believe that the real ætiological agent is the water (Ne buvez jamais d'eau), and since almost every Metro compartment is plastered with propaganda aimed at reducing the consumption of wine here is a conflict; but it must be said that Parisians bear the affliction without noticeable distress. However, the point is that they are intensely water-conscious; everywhere one sees taps labelled with the drinkability or otherwise of the water they dispense. This much is only to be expected and one might find it in any city in the world; but Paris is a French city, and perhaps there is nothing that makes this more plain than the large notice above a certain swimming-pool in the Seine, which announces that it is " Alimentée de l'eau potable ".

* * *

Hedgehog-lovers may like to know that, since I told you about William of Occam and my family coat-of-arms, I have been reading Isaiah Berlin's *The Hedgehog and the Fox*. This starts with the words: " There is a line among the fragments of the Greek poet Archilochus which says ' The fox knows many things, but the hedgehog knows one big thing '. Scholars have differed about the correct interpretation of these dark words, which may mean no more than that the fox, for all his cunning, is defeated by the hedgehog's one defence." Berlin uses this as a peg on which to hang his thesis that Tolstoi was an ambivalent character in whom the hedgehog and the fox were continually in conflict. It must have been very uncomfortable.

* * *

The senior partner is always altering his garden. He breezed into the practice office the other Monday. " Joan, I'm filling up that old well. Turn out the store-room and see if you can find anything which ought to be dumped." That evening he carried off two cartons of samples, five of obsolete case-records and official literature, a box of old instruments belonging to George, a broken filing cabinet, and a brass name-plate.

I wonder what excavating archæologists of 7000 A.D. will make of this bomb-proof outpost of the early N.H.S?

* * *

The old countryman, complaining of his indigestion, said: "I'm bringing up so much gas, doctor, I think it must be gasteritis."

* * *

REACTION

Seamus
When he was younger used
To listen to the atoms. Red
In the face from stooping
He'd declare
The little devils
Artful as a barrel-load of protons
Full of mischief
Just put two of 'em together
And the consequences!
Sure
They'll save us all a heap of work
So long as we provide
The most exorbitant
Ideal conditions
But
The more I listen
More I feel that work
Is mankind's
Only hope.

Letters to the Editor

TOO FEW DOCTORS

SIR,—In their article of Sept. 3 on the supply of doctors in Britain, Professor Lafitte and Professor Squire indicate that " unless there is immediate action, something like a crisis in the supply of doctors may emerge around 1965 ". Their reasoning appears to be irrefutable, and as there is little prospect of any immediate action, the prediction will doubtless be confirmed in due course.

The article is by implication critical of the reasoning and the assumptions of the Willink Committee. I think this is somewhat unfair because no indication is given of the politico-economic background to the appointment of the committee, which must have affected profoundly the basic premises with which the members approached their task.

In 1953 Mr. Guillebaud had been asked to investigate the cost of the N.H.S. and to advise how, in view of the burdens on the Exchequer, a rising charge could be avoided. Underlying the inquiry was the dissatisfaction of public and politicians with the excessive cost of the National Health Service and the heavy economic burden it represented. Long before the Guillebaud report was published, the Willink Committee was asked to consider whether or not the country was training too many doctors. It would have been almost inconceivable for the members to have suggested expansion of medical personnel when the whole nation " knew " that medical costs were already excessive.

We now know that the excessive economic burden of the N.H.S. is, and always has been, a myth. Indeed, in the years when the Guillebaud and Willink Committees were set up, the Health Service was absorbing a smaller share of the nation's resources than medical care had absorbed in Britain in the 1930s when financed by charity, local authorities, and patient payments. The Willink Committee did not know this at the time, and as it was largely composed of doctors, was hardly in a position to analyse the relevant economic data. Their information about the wider economic aspects of the N.H.S. would have been drawn from sources such as the *Times* and the *Economist*. What do these sources tell us of the economics of medical care?

The *Times*, on March 29, 1958, criticised the health service estimates for 1958–59 as excessive because the gross cost would rise by 40% from 1953–54 to 1958–69, while the retail price index was rising by only 20%. Although admitting that " health service costs have no close connexion with the trend of retail prices ", it considered that " the rising health bill has plainly gone beyond what price changes would justify ". This is curious reasoning, because medical care in the N.H.S. is not for sale, and therefore the concept of price is irrelevant—one must look at incomes, not prices. In addition, the year taken for comparison (1953–54) was the year when the proportion of national income absorbed by the N.H.S. was at its lowest—the trough which preceded the inevitable rise, as described recently.[1]

The *Economist*, on July 5, 1958, poured scorn on the suggestion " that the burden on the country's economy (had been) made no greater by the substitution of a publicly provided service for one that was privately paid for ". In search of economies it went on to wonder " whether money could not have been wrung out of (the hospital service) by a more realistic squeezing of hospital budgets ". The opinion of the *Economist* that a tax-financed health service costs more than privately financed medical care is a good example of the opinions which can be held when one does not bother to verify them by observation.

1. Seale, J. R. *Lancet*, 1960, i, 1399.

On reading these statements one wonders whether even the clear minds of the leader writers of the *Times* and the *Economist* become clouded by emotion when contemplating the prospect of actually paying for the Health Service. If this is so, it is hardly surprising that the doctors themselves are confused when considering problems intimately related to medical economics.

Richmond. J. R. SEALE.

MORE CHROMOSOME ABNORMALITIES

SIR,—May I comment on your leading article of July 23.

Sex chromatin is visible because it is positively heteropyknotic, which means that it is condensed and therefore stains intensely when the rest of the chromatin is relatively diffuse. But the phenomenon of heteropyknosis was actually discovered in the male. It was found at the beginning of the century that the X chromosome in the spermatocytes of insects "becomes greatly condensed and often rounded in form, stains intensely with basic dyes and thus appears as a karyosome or chromosome-nucleolus which shows the sharpest contrast to the thread-like or diffuse, and lightly staining ordinary chromosomes (autosomes)".[1] The two X chromosomes of the female do not show heteropyknosis. The same applies to mammals.[2] According to Schrader[3]: "Perhaps the most striking characteristic in the behaviour of the sex chromosomes is their heteropyknosis in the heterogametic sex, especially during the meiotic stages." He brings a considerable amount of evidence that heteropyknosis occurs when a chromosome has no homologous partner.

Recently interest has shifted to the sex chromatin of the female. It would seem as if the situation here is precisely opposite, since heteropyknosis occurs only if at least two X chromosomes are present. If a working hypothesis to cover the known facts is required at present, I suggest that it might be sought along the following lines. Heteropyknosis in the male occurs during meiosis, when the autosomes are paired and only the X chromosome is single. The sex chromatin of the female is seen only in non-dividing cells, where the presence of two X chromosomes results in heteropyknosis, possibly because the autosomes are unpaired. If one were to assume a slight difference in the timing of the two X chromosomes, one of them would become heteropyknotic in the presence of the homologous partner, but having done so, the second X chromosome has no homologue and therefore does not condense. This would explain Ohno's[4] demonstration that in female rats only one of the X chromosomes is heteropyknotic, as well as the fact that in diploid cells there seems to be one chromatin body less than the number of X chromosomes present.

Schrader[3] wrote in 1928: "All in all then we know astonishingly little about the cause of heteropyknosis. . . . Its answer no doubt involves a much more thorough knowledge of the structure and physiology of chromosomes than we now possess." In 1960 this is still true. But we know now that in different circumstances heteropyknosis may occur in cells containing a single X chromosome or in cells containing two X chromosomes, and this should be taken into account when formulating a hypothesis regarding the nature of sex chromatin.

Galton Laboratory,
University College,
London, W.C.1. URSULA MITTWOCH.

SHORTAGE OF RADIOGRAPHERS

SIR,—May I concur entirely with the remarks and suggestions put forward by Mr. Hutchinson (Aug. 20), and also propose that the same measures and views equally apply to the shortage of physiotherapists.

Sudbury,
Suffolk. DAVID WHITE.

1. Wilson, E. B. The Cell in Development and Heredity. New York, 1925.
2. Guenin, H. A. *J. Genet.* 1948, **49**, 23.
3. Schrader, F. Die Geschlechtschromosomen. Berlin, 1928.
4. Ohno, S., Kaplan, W. D., Kinosito, R. *Exp. cell Res.* 1959, **18**, 415.

OPERATING ON THE WRONG LIMB OR DIGIT

SIR,—The council of the Medical Defence Union is becoming increasingly perturbed by the number of occasions on which it is confronted with a patient's claim for compensation based upon the fact that an operation was performed on the wrong limb or digit. During the past twelve months the Union has dealt with no fewer than nine such claims and it is hardly necessary to say that cases of this sort are quite indefensible.

Such mistakes are not infrequently due to an error in the clinical notes—e.g., the word "right" instead of "left" is entered or, in the case of a finger or toe, the digit is wrongly numbered or described in the notes. The mistake is sometimes due to the fact that the wrong limb or digit is prepared for operation. In so far as the designation of fingers is concerned, the council reiterates[1] its suggestion that, in order to avoid any possible misunderstanding, the affected digit should be described as the "thumb", the "index finger", the "middle finger", the "ring finger", and the "little finger" and not as the "first", "second", "third", &c., finger.

In view of its recent experience the council of the Medical Defence Union considers it is only proper that the attention of the profession should be drawn to these unfortunate and avoidable mishaps.

PHILIP H. ADDISON
London, W.C.1. Secretary, Medical Defence Union.

TREATMENT OF PAIN IN PREAXIAL BORDER OF UPPER LIMB

SIR,—For a variety of reasons the article of Aug. 13 by Miss Wareham and Mr. Farrow was disappointing. This is a subject on which one would like to know more.

To begin with, it would have been interesting to know for how long and how frequently the traction was applied. Can the general practitioner use this method of treatment?

In most of such cases both the acromioclavicular and radiohumeral joints are involved to some extent, but they are not mentioned. They ascribe limitation of shoulder movement "to an associated adhesive capsulitis". Is this secondary to the cervical spondylitis, a neurotrophic phenomenon, or what? Capsulitis would suggest that there is an acute inflammation of the capsule amounting to an acute arthritis. If this were so the least movement would be excruciating. Anyway, such inflammations are unlikely to be secondary to lesions of the cervical spine. It is more likely that there is reflex motor irritation of the constituents of the musculotendinous cuff of the shoulder; but to describe this as adhesive capsulitis would be absurd.

Manipulation was mentioned, but not what sort, nor what objective results it achieved.

The possibility of symptoms arising from angulation of the nerve "around the neurocentral joint, and an excrescence from here . . ." is scarcely valid. If X-rays are repeated as soon as the patient is symptom-free, the appearances will be found to be unchanged. Osteophytic new growth or the osteochondrotic or sclerotic proliferation round chronically arthritic joints merely appears where there is room for it. (The use of the word neurocentral as applied to Luschka's joints implies that it is a defect of union between centres of ossification, whereas it is a joint between the uncinate process of one vertebral body with the body above. I thought they were called the unco-vertebral joints.)

Probably what their treatment has achieved is the relief of a group of restrictive joint lesions affecting the intervertebral joints of the fifth, sixth, and seventh cervical vertebræ. But one cannot be sure even of that, because the 14 lb. traction would be palpably effective down to the third or fourth cervical vertebra. For example, it is quite possible that the traction

1. Forbes, R. *Lancet*, 1955, ii, 774.

relieved a lesion of the first costovertebral joints which are sometimes more important than the cervical intervertebral joints in the ætiology of pain in the upper limb, though I am not too sure why.

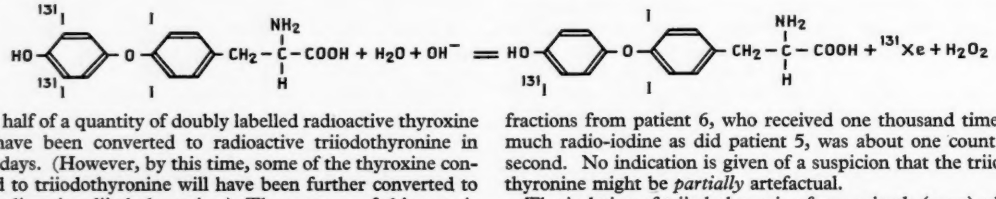
But the authors have left us without information on this. It is a pity that they could not at least have described the objective consequences of the traction. Have they at any time examined the amount of movement between individual vertebræ; or, more to the point, have they done so before and after treatment, so that they would know what they were doing? Almost all the things about which one would like to know more are the details of clinical examination. When the pathology is in doubt, the clinical picture is the only source of information.

Aberdeen. DUNCAN TROUP.

RADIOCHEMICAL SYNTHESIS OF TRIIODOTHYRONINE

SIR,—I should like to call attention to a correction which it might be necessary to apply to the results of certain published experiments performed with ^{131}I. These are experiments of several days' duration performed with thyroxine labelled with large amounts of carrier-free ^{131}I under conditions such that some thyroxine molecules will be doubly labelled.

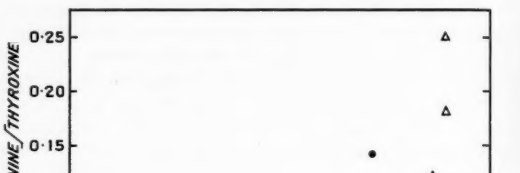
Radioactive decomposition of ^{131}I leaves an ^{131}Xe nucleus in place of the ^{131}I nucleus.[1] Xenon cannot, of course, remain as part of the molecule which was a thyroxine molecule but will become detached, taking with it the orbital electron which had been supplied by the carbon to which its parent isotope had been attached. The residuum of the thyroxine molecule will then have to react with a component or components of the solution in which it is dissolved. A possible reaction is given by the equation:



Thus half of a quantity of doubly labelled radioactive thyroxine will have been converted to radioactive triiodothyronine in eight days. (However, by this time, some of the thyroxine converted to triiodothyronine will have been further converted to non-radioactive diiodothyronine.) The purpose of this note is to call attention to reported experiments during which this conversion may have occurred. In the examples to be cited, correction was not made for errors possibly produced by this conversion, nor were control experiments performed to exclude the possibility of such a conversion.

In 1951 Gross and Pitt-Rivers [2] administered "100 mC of Na ^{131}I" to each of six human subjects. Since, in a subsequent paper,[3] these authors tabulate doses of radio-iodine as being either "mc." or "μc.", one must conclude that this dosage of ^{131}I in the first paper was expressed in millicuries. They chromatographed extracts of the blood-plasmas of these subjects and demonstrated two spots of unknown material concerning which they concluded ". . . that the entry of radioactivity into unknown 1 roughly follows that of thyroxine, whereas that into unknown 2 follows that of radioactive iodide". No unknown 1 was detected until two days after the administration of ^{131}I.

In a subsequent paper,[3] Gross and Pitt-Rivers identified unknown 1 as being triiodothyronine by means of two-dimensional and column chromatography. In this paper they stated that "the possibility that triiodothyronine might be an artefact of the extraction procedure was eliminated by adding tracer amounts of synthetic radioactive thyroxine to plasma and analysing the mixture on the column; fig. 2c shows that no triiodothyronine is formed under these conditions", but do not seem to have allowed time for the effect described above to be manifested. They also state: "That triiodothyronine may be a radiation artefact is unlikely for two reasons: (1) it was detectable in the plasma of patient 5 who had received only 100 μc. of radio-iodine; and (2) it has been isolated from the thyroid tissue of animals which had not received any radioactive iodine at all (unpublished)." No indication is given of the amount of triiodothyronine detectable in the plasma of patient 5, but it is perhaps noteworthy that the *peak* radioactivity of the column fractions from patient 6, who received one thousand times as much radio-iodine as did patient 5, was about one count per second. No indication is given of a suspicion that the triiodothyronine might be *partially* artefactual.



△ indicates data from table 2 and ● indicates datum from table 3 of Braasch et al. Arrow indicates ratio of aminoacids obtained from non-radioactive ox thyroid by Gross and Pitt-Rivers. Minimal overall time is that from administration of ^{131}I to determination of radioactivity in fractions and is in each case less than the actual duration by the time required for manipulations such as extraction and chromatography.

The isolation of triiodothyronine from animals (oxen) which had not received radioactive iodine was described the following year by Gross and Pitt-Rivers.[4] Nothing I submit in this note is to be construed as a criticism of their excellent work in this regard, but certain quantitative aspects of it will be pointed out below; and I should like to point out that the identification of radioactive 3,5,3^1-triiodothyronine in rat-thyroid hydrolysates, which they describe in the same paper, was performed on the thyroids of rats which had been given 100 microcuries of ^{131}I five days previously.

Since quantitative data on the relative amounts of triiodothyronine and thyroxine will help in an evaluation of the likelihood of occurrence of the postulated artefact, let us examine the data of Braasch et al.,[5] who administered 0·3–0·5 millicuries of ^{131}I to humans and after 48 hours hydrolysed specimens of their thyroid glands and determined the amounts of radioactivity in different fractions of these hydrolysates according to a slight modification of the kieselguhr-column procedure of Gross and Pitt-Rivers. In the accompanying figure I have plotted as Δ's the data of their table 2 (with the exception of two measurements they made on hydrolysates prepared in the presence of $Na_2S_2O_3$ and lacking triiodothyronine). The abscissa I have used is "minimal overall hours" or 48 plus the hydrolysis time, and the ordinates are the ratios of triiodothyronine radioactivity to thyroxine radioactivity. The arrow at zero overall hours is the ratio of triiodothyronine to thyroxine as isolated from ox glands.

1. Friedlander, G., Perlman, M. L., Stehn, J. R. General Electric Chart of the Nuclides. General Electric Research Laboratory, Schenectady, N.Y.
2. Gross, J., Pitt-Rivers, R. *Lancet*, 1951, ii, 766.
3. Gross, J., Pitt-Rivers, R. *ibid.* 1952, i, 439.
4. Gross, J., Pitt-Rivers, R. *Biochem. J.* 1953, **53**, 645.
5. Braasch, J. W., Flock, E. V., Albert, A. *Endocrinology*, 1954, **55**, 768.

All the points showing the presence of detectable triiodothyronine activity were obtained by enzymic hydrolysis, while 60% of the points showing no detectable triiodothyronine activity were obtained by alkaline hydrolysis. However, Braasch et al., in their table 3, describe an experiment in which the "column residual" fraction of an enzymic hydrolysis was rehydrolysed by alkali. This prolonged the minimum overall time to 116 hours and gave a triiodothyronine/thyroxine ratio of 0·14 (shown as ● in the figure).

These results are consistent with the existence of the error postulated at the beginning of this note. Inspection of the pertinent current literature reveals many papers to which the same criticism *might* be applicable but in which sufficient detail to determine whether or not this is so has not been supplied.

Please let me make this point clear. A single possible source of error is pointed out in this note. As examples of where this source of error may play a part, I have cited papers which undeniably are worthwhile contributions in several respects. Furthermore, there are many thyroid experiments performed with radioactive iodide which could not be affected by this error because of the presence of carrier iodide, short duration, or the ruling out of this effect by proper controls.

G. W. Carnrick Company,
Newark, New Jersey. MARSHALL E. DEUTSCH.

RADCLIFFE TRACHEOSTOMY TUBE

SIR,—It seems that, in one respect, Dr. Sandiford (Aug. 27) has misread our article of Aug. 20. Prototype A tracheostomy tube caused irritation, but when this was replaced by a tube *with identical measurements*, overdipped in latex (prototype B), the skin condition healed. The Radcliffe tracheostomy tube has been available with arms of two different lengths since 1956,[1] and for over eighteen months has been made in three.

Nuffield Department of Anæsthetics,
The Radcliffe Infirmary,
Oxford. R. H. SALT.

CEREBRAL MANIFESTATIONS OF ADDISONIAN PERNICIOUS ANÆMIA

SIR,—Dr. Fraser (Aug. 27) has most ably described a problem which must be more common than is generally realised. In 14 years of general practice in this area I myself have come across three such cases.

The first was a man of 54 who was admitted to a mental hospital as a typical case of endogenous depression of many months' standing. The correct blood diagnosis was made in hospital and injections of 'Anahæmin' alone raised the depression. He has kept well ever since and had regular injections of vitamin B_{12}.

The second was a case of depersonalisation in a woman of 43. She had in the first instance six months' treatment in a mental hospital without any benefit. Later at home she developed extreme pallor with an icteric tinge, and she was diagnosed as a case of pernicious anæmia at the general hospital. Vitamin-B_{12} injections have given her a normal blood picture, but her mental state has remained just the same.

The third case was a woman of 53 who was a depressed diabetic. She had been in a state of depression for years. Pallor and paræsthesiæ developed and the local diabetic clinic diagnosed pernicious anæmia with subacute combined degeneration. She was given vitamin B_{12} and this cleared her anæmia, paræsthesiæ, and depression, and she has been remarkably well ever since.

In all three cases the mental symptoms developed long before the blood picture became obvious. Under the circumstances it is fortunate that two out of the three made such a good recovery. How long can pernicious anæmia lie latent? A friend of mine lost his father and his grandfather from pernicious anæmia. In middle age this man began to feel ill with intense lassitude and diarrhœa. With such a family history his physicians must have looked for pernicious anæmia, but it was some four years before the blood-count revealed the true diagnosis. He has been perfectly well since the institution of vitamin-B_{12} treatment.

All this makes one wonder how many more chronic cases in general practice are suffering from latent pernicious anæmia. We are rightly advised not to give B_{12} until a precise diagnosis has been made, but the temptation to give some of these patients "a shot in the arm" is very real. How accurate are the methods of early diagnosis advocated by Dr. Fraser, and how soon will they be available to our patients?

Ibstock, Leicestershire. C. A. H. WATTS.

1. *Lancet*, 1956, ii, 1247.

DOUBTFUL PROGRESS IN PSYCHIATRY

SIR,—The balanced and judicious comments by Dr. Oliver (July 30) are indeed timely and deserve very careful consideration. Those of us who have been privileged to gain our early experience in the most progressive mental hospitals, and have also acquired an eclectic psychiatric orientation—comprising individual and social psychological, as well as organic and physiological, concepts—and whose outlook is consequently far from "reactionary" or overcautious, have nevertheless all too often been faced, for various reasons, with the dilemma of steering a treacherous course between the Scylla of institutionalisation and the Charybdis of discharging prematurely our psychotic patients.

The social and legal problems which confront us are apparent in the following statement[1]:

"It is necessary to balance the possible benefits of treatment or training, the protection of the patient and . . . of other persons, on the one hand, against the patient's loss of liberty on the other"—although in practice this is sometimes easier said than done, depending as it does on clinical judgment and experience, and too often also on administrative expediency. It is no doubt true, as Professor Hargreaves [2] says, that those requiring compulsory detention are "a minority of about 20% of the patients who enter mental hospitals", but it remains primarily the onerous responsibility of psychiatrists to ensure that these 20% are cared for in hospital as long as may be necessary, and that the community is also reasonably protected so far as some of these patients are concerned. Taking the figures for 1955, for England and Wales alone, 20% of admissions to mental hospitals still represent some 19,500 patients, and 20% of the mental hospital population, some 30,700 patients; and, in addition, it should be noted that, in 1954, second or subsequent admissions to mental hospitals were equivalent to approximately two-thirds of new admissions during the same year (63% for males, and 69% for females).[1]

It is of interest that the main points raised by Dr. Oliver are emphasised in almost identical terms in a recent article by a French psychiatrist,[3] in which he draws attention to a large series of serious crimes of violence committed in France in the past few years by prematurely discharged mental patients (without, as the author observes, taking into account the numerous suicides and other tragedies attributable to this same cause). Many patients thus "sacrificed to administrative expediency" and the policy of rapid turnover are subsequently readmitted to hospital on a number of occasions, each time a little more deteriorated.

Leconte concludes that the present situation, in France, appears to be "serious not only for public order and personal safety, but for the mental patients themselves who, when

1. Report of the Royal Commission on the Law relating to Mental Illness; pp. 110, 310–311. Cmd. 169. H.M. Stationery Office, 1957.
2. Hargreaves, G. R. Psychiatry and the Public Health; pp. 113, 68–71. London, 1958.
3. Leconte, M. *Ann. Méd. lég.* 1960, **40**, 246.

really cured, will once again see closing before them the doors which were beginning to open, but which one has no right to open forcibly, or surreptitiously ".

There is undoubtedly a need for reappraisal of the clinical and administrative criteria for discharge (on trial or otherwise) of psychotic patients from mental hospitals, combined with an objective, statistically representative, follow-up survey of such patients. Most important of all, at the present time, is the lack of continuity of the treatment in hospital of the psychiatric patient, and subsequent provision, so far as it may exist, for his " aftercare ". As Hargreaves [2] states, " on discharge from hospital, the patient's aftercare, resettlement, and rehabilitation was made a function of the local authority by the same Act which removed from it the administration of the mental hospitals. This function was not made an obligation of the local authority. . . . Small wonder that this aspect . . . should have been largely neglected. . . . How can continuity of care be provided for the psychiatric patient with such a division of responsibilities between authorities whose boundaries bear no relationship to each other ?"

As, for example, in the case of psychiatric reports for juvenile courts, it is not only useless but also highly detrimental to the patient and society alike to make recommendations that cannot, in practice, be implemented; and it is futile and potentially dangerous to take for granted, for reasons of administrative expediency divorced from clinical judgment, the existence, magnitude, and efficiency of services and facilities that are, for the most part, not in fact available, and for which, indeed, apart from the many other obstacles, there is such a deplorable lack of adequately trained, specialised personnel.

Bransgore, Hampshire. R. H. AHRENFELDT.

OCCAM'S RAZOR

SIR,—Your interesting annotation of Aug. 6 mentions that the learned inaccuracy *Entia non sunt multiplicanda praeter necessitatem* is still given in a vast transatlantic publication. It is, perhaps, worth noting that it is also still given in the *Oxford Book of Quotations*.

Kingsdown, Deal, Kent. W. B. ROANTREE.

OUR POOR THAMES

SIR,—Mr. Longmore and Dr. Thompson's conclusions (Aug. 20) refer to a part of the river considerably nearer to the mouth than the districts of which I am M.O.H.; nevertheless I have had samples as polluted as theirs without being able to convince myself that the river could on that account " constitute a major menace to public health ". On the contrary I have recently advised one of my councils in the following terms:

" Although no one can guarantee that no case of infectious disease could ever occur through river bathing, the risk is in my view infinitesimal, certainly no greater than that of being knocked down crossing the street or of getting food poisoning any time one buys food in the open market. Finally, although I have been for nearly fourteen years a Medical Officer of Health of riverside authorities with bathing places, I have never known any case of illness attributable to bathing in the river, and in my view the pleasure and healthful effects of bathing very far outweigh any risk involved."

I have spoken to many doctors, but I have yet to find one who can quote me a single case of typhoid, poliomyelitis, or even Weil's disease which could reasonably be presumed to have its origin in the ingestion of river water. Can Mr. Longmore or Dr. Thompson produce any such evidence?

The pollution of sea beaches which touched off their alarm is, everyone agrees, revolting and inexcusable from the amenity point of view, yet no one, so far as I know, has been willing to come forward and say it constitutes a public-health risk.

There are so many graver dangers which an M.O.H. must bring to the notice of the inhabitants of his area that he should, I feel, be most careful in crying wolf over remote and theoretical possibilities.

HECTOR MACKENZIE-WINTLE
Medical Officer of Health,
South Oxfordshire Combined Districts.
Oxford.

UNITS

SIR,—May I plead for uniformity in the use of units? In a recent paper the fluid balance of a patient was quoted as (*a*) pints intake and (*b*) millilitres urinary output. In *The Lancet* of Sept. 3 (p. 527) I am introduced to a unit with which I am unfamiliar, the square foot-millimetre, to designate the area of a dialysing surface. If you think that we should still measure things in minims, fluid ounces, and pints; grains, scruples, and ounces; inches and feet, I shall respect your opinion. However, having been brought up as a scientist, I find these units irrational and so expensive in calculating time that, in company with European colleagues, I am sometimes discouraged from trying to understand publications which employ them.

Department of Biochemistry,
The Royal Infirmary,
Glasgow. JAS. C. EATON.

ACUTE HÆMATOGENOUS OSTEOMYELITIS

SIR,—That early diagnosis and an effective antibiotic, in effective dosage, would render any form of surgical operation unnecessary in some cases of acute hæmatogenous osteomyelitis, was prophesied by Florey and Florey [1] 17 years ago. The conditions under which this prophecy could be fulfilled were defined in pathological terms by Trueta and Agerholm [2] 12 years ago. But this important possibility has been either doubted or not seriously discussed in two recent editorial comments [3 4] on the treatment of the disease.

Having seen many cases in which the Floreys' prophecy has been fulfilled in practice, we have attempted to define [5] in clinical terms the conditions under which such a result could be expected. Even in the severe form of the disease we found that 9 out of every 10 patients whose treatment with an effective antibiotic in adequate dosage was started within forty-eight hours after the onset of the pain showed rapid and complete healing without any form of operation: whereas pus had to be removed surgically (by aspiration or by open operation) in 6 out of every 7 cases whose effective antibiotic treatment was started after the first forty-eight hours. Also, serious complications, such as septic arthritis, were almost confined to these late cases.

The first forty-eight hours after the onset of the pain therefore seems to be of crucial importance. We regard it as the target period within which the family doctor should aim to make the correct diagnosis (or suspect it), and refer the patient to hospital, where he can be adequately investigated, treated with antibiotics in adequate dosage (e.g., injection every three hours initially), and operated upon if this should after all prove necessary. We know that about three-quarters of the patients whom we see here have sought medical advice within these critical first forty-eight hours, and we are most grateful to the many family doctors whose prompt actions have made it possible for us to see the Floreys' prophecy so often fulfilled. Their patients have good reason to be grateful to them too.

1. Florey, M. E., Florey, H. W. *Lancet*, 1943, i, 387.
2. Trueta, J., Agerholm, M. *Post Grad. med. J.* 1948, **24**, 229.
3. *Brit. med. J.* 1960, i, 537.
4. *Lancet*, Aug. 20, 1960, p. 415.
5. Bremner, A. E., Neligan, G. A. Recent Advances in Pædiatrics (edited by D. Gairdner); chapter 13, p. 364. London, 1958.

Neglected osteomyelitis remains a surgical disease, we agree, and removal of pus from the subperiosteal space is surely a matter of some urgency. But it seems to us more important to recognise that diagnosis within the first forty-eight hours, and immediate transfer to hospital as an emergency, offers a very good chance of avoiding all that, and of achieving rapid healing with return to full activity in a matter of weeks.

The Childrens Clinic,
Royal Victoria Infirmary,
Newcastle upon Tyne.

A. E. BREMNER
G. A. NELIGAN.

MEDICAL SERVICES IN SOUTHERN RHODESIA

SIR,—The contribution of Dr. Stott (Aug. 27) to The Wider World has aroused my nostalgia. I spent a year in practice in Southern Rhodesia as a young graduate. I have never regretted this sojourn, and I have often regretted my failure to settle permanently in Rhodesia. I am glad to learn that there are still opportunities there for the adventurous young man, and I commend Dr. Stott's suggestion that service in Southern Rhodesia would represent a real contribution to better race relations. It would be interesting to have some idea of the numbers of African doctors who have been recruited up to now, and the numbers who may become available over the next ten years or so. There is perhaps a tendency to exaggerate the size of the possible reinforcement. The letter of Professor Davies (Aug. 27) draws attention to a similar field for over-estimation.

St. Mary's Hospitals
for Women and Children,
Manchester.

W. I. C. MORRIS.

EXPIRED-AIR RESUSCITATION

SIR,—Since you published my letter in May,[1] describing regurgitation after the application of the mouth-to-mouth method of artificial respiration, a colleague of mine has had a similar experience.

He was called to a collapsed patient who had ceased breathing and whose pulse was scarcely perceptible. He used mouth-to-mouth resuscitation for some minutes—perforce intermittently because of the need to clear the mouth of regurgitated vomitus. He turned the patient on to his chest and continued with the Holger-Nielsen method. The patient died despite his efforts. My colleague was quite revolted by the task he set himself and considers the regurgitation, quite apart from its intrinsic danger, a severe æsthetic drawback to this method.

I was myself present recently at the revival of a 19-stone man who had been overcome by hydrocarbon vapour in a ship's tank, and with delay and difficulty rescued. Holger-Nielsen artificial respiration was performed with the eventual recovery of the victim. He was for some time blind after the event, which would indicate a severe degree of cerebral damage, fortunately reversible. The efficacy of the Holger-Nielsen method, under field conditions, is particularly well shown.

On the strength of my own knowledge of the effect on the stomach of mouth-to-mouth resuscitation, I would not now use it until I was convinced that regurgitant vomitus in the oropharynx is of no consequence to an apnœic person.

It seems likely that peak pressures achieved by this method overcome the resistance of the cardiac sphincter and cause the regurgitation. Mouth-to-nose breathing, advocated by Dr. Henning Ruben,[2] would appear to overcome this objection.

Medical Department,
Esso Refinery,
Fawley, Southampton.

G. MATTHEWS.

1. *Lancet*, 1960, i, 1070.
2. Ruben, A., Elam, J. O., Ruben, H. *ibid.* 1959, ii, 69.

VALUE OF A LARGE DOSE OF ANTITOXIN IN CLINICAL TETANUS

SIR,—The paper of July 30 by Professor Brown and his colleagues suggests that Jamaican children were included in the clinical trial. In fact neither I nor my pædiatric colleagues in Jamaica considered it justifiable to withhold antitoxin from our patients with tetanus, because we were firmly convinced of its value.

At the University College Hospital of the West Indies few cases of tetanus are seen and the experience of the disease is far less than in Ibadan. The standard treatment is 100,000 units of antitoxin for neonates and 200,000 units for other children, half the dose being usually given intravenously. Sedation is achieved by chlorpromazine and phenobarbitone, the dosage being carefully controlled according to the clinical condition of the patient.

During the past five years 27 cases of tetanus have been treated in the children's ward of whom 10 died. 5 out of 8 cases of tetanus neonatorum died; if these are excluded the mortality of children is 5 out of 19. The mortality of 26% in this small series compares with 49% for Brown et al.'s patients treated with antitoxin and 76% for those not treated with antitoxin. I should like to pay particular tribute to the house-officers and nursing staff of the University College Hospital whose devoted care enabled so many of the children to survive.

University College Hospital of The West Indies,
Mona, St. Andrew, Jamaica.

E. H. BACK.

HYDROCORTISONE BY INHALATION

SIR,—I was interested by the paper in your issue of Aug. 20 by Dr. Langlands and Dr. McNeill, in which they report the absence of any improvement, as regards respiratory function tests, in 10 patients with chronic asthma, when treated with hydrocortisone-acetate inhalations for a month. I agree that the results of this therapy in chronic asthmatics are often disappointing, but I do not think it is necessary to conclude from this investigation that hydrocortisone inhalations are of no value, and have no place in the treatment of asthma.

10 patients is a small number from which to draw definite conclusions, and they appear to have been an unfavourable group having suffered from asthma for periods of between 12 and 26 years, some having emphysema, and 4 having $^1/_2$ oz. of sputum daily. In spite of this, 4 patients had subjective improvement on the hydrocortisone and only 1 on the placebo, which is about the relative proportion I would expect in this group. I do not think it need be concluded that this subjective improvement was necessarily a chance finding or due to the " tonic " effect of the inhalation of 15 mg. of hydrocortisone daily (perhaps half being absorbed), simply because the respiratory function tests estimated once or twice a week showed no parallel improvement. The patients, no doubt, assessed their symptoms throughout the 24 hours of every day of treatment and possibly some were especially liable to nocturnal attacks of wheezing. Brockbank and Pengelley [1] obtained significant results in a double-blind controlled trial using extremely small doses, which surely eliminates the " tonic " effect as a substantial factor. I agree that respiratory function tests may be very valuable in assessing the results of treatment in chronic asthma but I do not think they are always necessary or justifiable in acute asthma. Some of our patients [2] were experiencing fairly severe continuous asthma during the trial, and the response to hydrocortisone as opposed to the placebo, and also to routine antispasmodics, &c., was sometimes dramatic and incontrovertible.

I have come to use hydrocortisone powder inhalations infrequently for asthmatic patients, not because they have no effect but because they are usually much less effective than systemic corticosteroid drugs, the dangers of which would

1. Brockbank, W., Pengelley, C. D. R. *Lancet*, 1958, i, 187.
2. Helm, W. H., Heyworth, F. *Brit. med. J.* 1958, ii, 768.

appear to be small if used in the minimal effective dose and, where possible, intermittently. I believe, however, that these inhalations have a small place in the treatment of recurrent acute asthmatic attacks and in exacerbations of chronic asthma especially if there are contraindications to systemic therapy such as gastric ulceration or hypertension.

Chest Clinic,
The Marsden Hospital,
Burnley. W. H. HELM.

ATHEROSCLEROSIS AND CORONARY HEART-DISEASE

SIR,—Dr. Gresham and Dr. Howard (Sept. 3) have fed rats on a diet containing 40% butter, and have noted massive thrombotic phenomena. If a human being received a diet of which, God forbid, say, 1500 calories a day were derived from butter, and fed this until his premature death from obstructive thrombosis of the cardiac chambers, aorta, coronary arteries, and renal veins (by no means certain), could we then assume, as the authors seem to have done, that coronary thrombosis in an individual eating a reasonable amount of butter does not require previous damage of the coronary arteries by atherosclerosis?

Public Health Offices, Ilford. I. GORDON.

TUBERCULOSIS: A SOCIAL STIGMA

SIR,—When will the medical profession realise that tuberculosis is more than just a disease? Is it not obvious that many people regard tuberculosis as a social stigma, equal in many ways to a prison record? The fact that legal pressure has often to be placed on a sufferer, to force him to take treatment, should be an indication of the truth of this statement.

I am not a doctor, but four years of sanatorium life has, I believe, qualified me to comment on this subject. So also has my experience of the many difficulties an ex-patient has to face on his release from hospital.

It is strange perhaps, but true, that even in hospital up to 20% of tuberculous patients are still not prepared to admit that they are suffering from the disease. Many doctors would be surprised to know how many cases of asthma, bronchitis, or (incredible but true) worms in the chest they have wrongly diagnosed as tuberculosis. I have even known patients who have falsified their temperatures, vomited medicine, and spilt tea or other covering liquids into sputum cups which held traces of blood.

There may be many reasons for such peculiar behaviour, but perhaps the main one is that most patients know that when they are released from hospital, they enter a class of unwanted, and in most cases unhelped, people. They know that they will never be able to obtain a position which involves a medical check-up, unless they can bluff their way through. They know that if a job is superannuated, they have little chance of acceptance.

What is far worse, they know that their friends will regard them with suspicion, and often even avoid them altogether. In more than one unfortunate case, marriages have broken up, especially where one parent has been afraid for his or her children. Is it then any wonder that many patients fool themselves, and believe that they are fooling others?

What is needed today is a re-education campaign, directed at all sections of the public. People must be made to realise that it is possible for anyone to contract tuberculosis, and that there need be no shame attached to it. There should, also, be a more realistic approach on the part of the Government to the question of National Assistance payments to the families of tuberculous breadwinners. At the present time, the rates are ridiculously low (especially in view of the fact that the whole family may be regarded as contacts and therefore in need of added sustenance). Not until this is done will the time come when the threat of court orders, &c., will no longer be necessary.

Liverpool. M. S. FOSTER-MOORE.

ORAL HYPOGLYCÆMIC AGENTS

SIR,—Two cases of coma recently admitted to our special poisons unit will be of interest in view of your recent correspondence on chlorpropamide. Coma from this cause or due to related substances might not unreasonably be expected to occur with greater frequency during the next few years.

CASE 1.—A woman of 58 was admitted early this year in coma. It was known that she had been given a small supply of barbiturates. She had been depressed and unable to sleep since the death of her husband some four weeks earlier. Examination revealed faint cyanosis, skin dry and cool, shallow respiration at rate of 12 per min., blood-pressure of 90/70 mm. Hg, and an oral temperature of 98°F (36·7°C). Routine biochemical examination of her blood was normal and no barbiturates could be detected in stomach washings, blood, or urine. She recovered consciousness in 48 hours but was not very communicative, it being, however, presumed that she had taken more sleeping capsules than was intended.

She was readmitted some three months ago in coma of about 6 hours' duration. When she was discovered, a note beside her left no doubt that this time she was deliberately taking an overdose of tablets to end her life, and an empty unlabelled container was found in the room. The findings were similar to those of the earlier admission, but reflexes were completely absent, respiration was shallower and slower (200–300 ml. per respiration at 10 per min.), and the blood pressure lower (70–80/50–60 mm. Hg); and she was obviously more profoundly collapsed.

Emergency treatment was immediately instituted, consisting of the usual maintenance measures, including a continuous intravenous drip of 0·9% vanillic acid diethylamide in 5% glucose solution as a respiratory stimulant. Again the biochemistry of the blood was normal and no barbiturates or other sedative could be detected in stomach washings, blood, or urine. In spite of increasing respiratory volume to 450–600 ml., respiration-rate to 16–20 per mm., and blood-pressure to 100–120/60–70 mm. Hg and occasional return of cough reflex, the patient remained unconscious after 24 hours. Repeated biochemical examination of the blood and urine revealed no barbiturate nor any of the commoner drug causes of coma. Intravenous medication was continued during the prolonged coma, and a later fall in blood-pressure was temporarily controlled by L-noradrenaline. After 96 hours of coma the patient died. At the inquest it was suggested after inquiry that this patient had taken her husband's oral hypoglycæmic tablets since these were the only tablets available and she had received no further supply of sedatives or barbiturates from her doctor.

CASE 2.—A woman of 57 was admitted in coma. She was slightly cyanosed, her skin was cool and dry, her respiration shallow (250 ml.) and slow (11 per min.), body-temperature 97·6°F (36·5°C), blood-pressure 90/60 mm. Hg, complete areflexia, and pupil 5 mm. in diameter. This patient had apparently been disorientated for 3 days before onset of coma some few hours before her admission. She was a known diabetic controlled on 750 mg. of chlorpropamide daily.

Biochemical examination of her stomach washings, blood, and urine revealed no barbiturate or other hypnotic cause of her coma. Blood chemistry was normal, but the blood-sugar level was 75 mg. per 100 ml., and fell to 50 mg. per 100 ml. Intravenous glucose solution sufficient to elevate her blood-sugar to well over 250 mg. per 100 ml. and produce glycosuria nevertheless produced only very slight immediate improvement in her physical condition. A continuous infusion of 0·6% solution vanillic acid diathylamide in 5% glucose was administered to maintain an adequate minute volume of respiration. It was necessary also to maintain for 96 hours continuous glucose infusion to sustain an elevated blood-sugar

level. She recovered from her coma after 3 days and entered a stuporous state which lasted some 6 or 7 days, during which time she was hardly cooperative, though only drowsy. When fully recovered this patient had complete amnesia for the period extending from 72 hours before admission to 9–10 days after admission—i.e., for the entire duration of stupor and coma.

The outstanding feature of both these cases was the identity of clinical state between these patients and those in barbiturate coma and the absence of the dramatic recovery that one would usually expect in any case of hypoglycæmia treated adequately with parenteral glucose solutions.

Poisons Unit, Oldchurch Hospital, Romford, Essex. S. LOCKET
I. P. BROWN.

STERILISATION OF THE DIABETIC'S SYRINGE

SIR,—Must it be sterile? My experience dates from 1926 and for many years now I have kept the assembled syringe and needle dry in a vulcanite case.

I pull the plunger out to the required mark, push the needle through the untreated rubber cap, withdraw the insulin, and inject it. I blow out with the plunger any remaining drop, and put the assembled syringe and needle back into the vulcanite container. All this takes about 60 seconds. I do not touch the needle except at the hilt to hold it firm, and I have long ago discarded the metal top of the syringe.

When a bruise appears at the site of injection after many months, I have a new needle. Apart from this there is no sign visible to the naked eye that injections have ever been made, and not the slightest infection has arisen.

A year or two I drew the distal end of the needle in use over a culture-plate; a rich growth of *Staphylococcus aureus* developed. One must be immune to one's own staphylococci.

Hove. G. M. WAUCHOPE.

HYPOKALÆMIA, CARCINOMA, AND CUSHING'S SYNDROME

SIR,—I read Dr. Bagshawe's article of Aug. 6 with interest in view of a patient who was recently in this hospital and whose diagnosis at the time of his first admission gave rise to considerable discussion because of the unusual association of some of the features of Cushing's syndrome with low serum-potassium and unexplained œdema.

A man, aged 60, in July, 1956, first attended hospital having had two months' swelling of the ankles. No renal, nutritional, or cardiac cause was found to explain this. July, 1957: recurrence of œdema not now disappearing on bed rest; again no cause found. January, 1958: first noticed bruising of skin and œdema became worse.

July, 1958: admitted to hospital under Dr. E. R. Cullinan. Looked well. Fundi normal. Soft right axillary node palpable, otherwise no lymphadenopathy. Pulse 76, regular. Blood-pressure 175/90 mm. Hg. No cardiac enlargement. Abdomen obese. Liver, spleen, and kidneys not palpable. No other mass. Central nervous system normal. Skin showed (*a*) purpuric spots and patches over trunk and arms, (*b*) some small pigmented papillomata, (*c*) a few Campbell de Morgan spots, and (*d*) some flat pale brown plaques over chest.

Hæmoglobin 82%. White blood count 8400 per c.mm. Platelets 161,000 per c.mm.

Serum-proteins total 5·1 (albumin 3·8, globulin 1·3) g. per 100 ml. Serum-sodium 146 mEq. per litre. Serum-potassium 2·8 mEq. per litre. Serum-chlorides 101 mEq. per litre.

Glucose-tolerance curve diabetic in type.

Basal metabolic-rate −8%.

24-hour urine specimen: 17-ketosteroids 15·0 mg. per day; 17-hydroxycorticoids 37·6 mg. per day. The amount of beta-17-ketosteroid excreted was within lower limits of normal range.

Calcium excretion 495 mg. per 24 hours (normal 120–270 mg. per 24 hours).

Chest X-ray showed fractures of right 5th and 6th ribs, and rather thickened costochondral junctions.

X-ray lumbar spine showed compression collapse of D12.

Erythrocyte-sedimentation rate 2 mm. in one hour.

A presacral air insufflation was attempted but was unsuccessful because he was unable to walk owing to D12 collapse.

Corticotrophin was given and the 17-ketosteroids rose to 24 mg. on the fourth day and 17-hydroxycorticoids rose to 92·5 mg. on the fourth day.

These investigations showed that he had some of the features of Cushing's syndrome:

(1) Osteoporosis with spontaneous fracture.
(2) Diabetes mellitus.
(3) Purpura.
(4) Increased adrenal steroid output.

In addition, he had a low serum-potassium and a high serum-sodium.

A diagnosis was made of adrenal hyperplasia, and in view of his deteriorating general condition the adrenals were explored on Oct. 24, 1958. They were moderately enlarged. The whole of the left adrenal was removed and four-fifths of the right. Histological section showed the changes of Cushing's syndrome; there was no hypertrophy of the zona glomerulosa to suggest Conn's syndrome.

Postoperatively his œdema rapidly disappeared and it was then obvious that his muscles were extremely wasted and he was unable even to lift his leg up from the bed. Subsequent progress and investigation showed him to be in positive nitrogen balance and in normal calcium and potassium balance. He was given testosterone, and a maintenance dose of cortisone 12·5 mg. b.d. was reached by Nov. 28.

On Dec. 12 he developed pneumonia (after a prevalent influenza epidemic) and after twenty-four hours suddenly collapsed, his blood-pressure falling to 70/20. This was considered to be an adrenal crisis and responded only to hydrocortisone in combination with noradrenaline. He rapidly recovered from a state of collapse but since that time a return of his œdema had been noticed; serum chemistry remained normal, and diuretics had moderate response. At the time of discharge there was no evidence of diabetes; but œdema of the ankles and hands was still present. He was able to walk with a spinal corset and sticks.

His condition remained much the same until May 11, 1959, when he noticed intermittent central abdominal pain. This persisted for two weeks and on May 25, 1959, he was admitted with severe abdominal pain in a state of collapse. A diagnosis was made of intestinal obstruction, but he was not fit for surgery and he then perforated. Serum-sodium 145 mEq. and serum-potassium 3·7 mEq. at this time. In spite of rigorous therapy he did not improve and died on June 7, 1959.

Necropsy (Dr. A. G. Stansfeld).—The body was well-nourished, though the state of nutrition was partly masked by gross subcutaneous œdema affecting not only the lower limbs but the trunk and upper limbs. There was marked muscular wasting of the peripheral limb muscles but abundant subcutaneous fat over the trunk.

Abdomen: Diverticulitis of colon. One diverticulum in ascending colon had perforated. Suppurative peritonitis with abscess in lower abdominal cavity.

Liver: 2770 g. Multiple secondary nodules of carcinoma.

Neck: enlarged nodes in both supraclavicular fossæ, large node replaced by growth in right paratracheal region.

Remaining portion of right adrenal had undergone hyperplasia, weight now 7·5 g.

Section of the paratracheal node showed a highly cellular and clearly malignant neoplasm. Most parts of the growth lacked distinctive features, but the appearances of the tumour favoured the supposition that it was a primary neuroblastoma arising from the sympathetic chain at the thoracic inlet. Sections of the liver showed numerous metastatic deposits of a cellular malignant neoplasm resembling the growth in the neck. (Examination of the head and brain was not permitted.) The adrenalectomy was done through a posterior approach and so it is impossible to say whether liver metastases were present then or not.

If the neuroblastoma is to be considered the cause of the adrenal manifestations then he must have had this for over three years before death, and yet there was no involvement of the adrenals themselves with growth.

St. Bartholomew's Hospital, London, E.C.1. J. A. PARRISH.

Obituary

GORDON GORDON-TAYLOR

K.B.E., C.B., M.A. Aberd., M.S., B.Sc. Lond., LL.D., Sc.D., F.R.C.S., F.R.A.C.S., F.A.C.S.

THOUGH he had become almost a legendary figure, Sir Gordon Gordon-Taylor at 82 was still very much part of the medical scene, and the news of his death on Sept. 3 will bring real regret to the many people all over the world who liked and admired him so much. One of the most brilliant surgeons of his day, he became in later years a spokesman and ambassador of British surgery. He was still, as always, both a stimulus and a support for younger men, and indefatigable in his help to Commonwealth and foreign students visiting this country.

Gordon-Taylor was born in Aberdeen and was educated at Gordon's College and the University, where he graduated in arts in 1898. The same year he moved south and entered the Middlesex Hospital with a scholarship. Having qualified in 1903, he became demonstrator in anatomy under Peter Thompson; and in that year, when the University of London instituted an honours degree in anatomy (B.SC.) he and Victor Bonney were the first candidates. They worked long hours into the night, heating coffee essence on a bunsen burner to sustain them, and attained first-class honours. This interest in anatomy he retained all his life; and he continued to add to his qualifications by gaining the M.S. Lond. and the F.R.C.S. in 1906. In the following year, at the age of 29, he was elected to the staff of the Middlesex Hospital as an assistant surgeon.

Central Press Photos Ltd.

It was round the Middlesex Hospital that most of Gordon-Taylor's work centred. He served other hospitals too, including for a time the Royal Northern; but the Middlesex was his home. He was assistant to Pearce Gould, and to Bland-Sutton who influenced his early career; and by the outbreak of the 1914–18 war he was recognised as an established and very able surgeon. During this war he served in casualty-clearing stations, gaining great insight and experience in major abdominal surgery, and was appointed consultant to the 4th Army.

On his return to the Middlesex he brought back many ideas —such as the use of blood-transfusions, given in those days with a Kimpton tube—which enabled him to develop and expand the scope of his surgery. In 1920, on Bland-Sutton's retirement, he became full surgeon to the hospital and undertook one of the busiest practices in London. At the Middlesex he operated on three afternoons a week—including Saturdays, so that foreign visitors from abroad need not feel that British surgery had adopted a weekend attitude! During the '20s and '30s he worked and wrote on many aspects of surgery. Many of them were connected with cancer—of tongue, breast, colon, and stomach; others were more general, such as parathyroid and carotid-body tumours. But two of his great subjects were reserved for later years—innominate aneurysm, published when he was 72, and hindquarter amputations, which he carried out in the years of his so-called retirement. His hundredth was successfully performed when he was 80.

From the outbreak of the late war Gordon-Taylor served in the Royal Navy with the rank of surgeon rear-admiral. His territory covered south-east England, and in the period of air-raids he was actively operating and advising on casualty work. His former experience with war injuries was invaluable, but he was one of the first to modify his approach in the light of changing conditions. His duties involved travelling, and he visited many countries during the war years. He was one of the group of surgeons who visited Russia and conferred diplomas of the Royal College on Russian colleagues. The Pacific Fleet saw him in 1945.

His time at the Middlesex was up before the end of the war, but for Gordon-Taylor retirement was a misnomer. It was the start of a new phase of his surgical activities. Active in mind and body, he continued to dazzle friends and associates by his operative skill, while in public life more and more demands were made on him as teacher and speaker. He lectured in many places—Cairo and Toronto, Leeds and Cardiff, Harvard and Melbourne, Athens and Münich, Lahore and Edinburgh. He acted twice as professor of surgery in the Peter Bent Brigham Hospital and as a postgraduate professor in Cairo. He was president of the Association of Surgeons, of the Royal Society of Medicine, and of the Medical Society of London. Surgeons in France, Belgium, Greece, Germany, Norway, and Denmark welcomed him with honour. The United States accorded him the distinction of commander in the Legion of Merit. He examined in many countries and universities; but what he perhaps liked best was examining in anatomy for the primary F.R.C.S., which in one way and another he undertook for many years.

The Royal College of Surgeons was an abiding interest. He was elected to the council in 1932 and was vice-president in 1941–43. Three Hunterian professorships were accorded him, and as vice-dean of the Institute of Basic Medical Sciences he was counsellor to the young visiting surgeon until the day of his death. His Bradshaw lecture and two Vicary lectures at the college were memorable occasions. He was an honorary fellow of the colleges of surgeons of Australasia, America, Canada, Ireland, and Edinburgh; an honorary member of the surgical societies of Belgium, Norway, Greece, France, and Germany; and an honorary graduate of the universities of Toronto, Athens, Melbourne, and Cambridge. Of these distinctions two, perhaps, gave him particular pleasure—the doctorate of science given to him at Cambridge by his old friend Lionel Whitby and the fellowship of the surgical college of his native land. The gold medal of the Royal Society of Medicine was a unique distinction that he received recently, and signal honours were bestowed on him by the *British Journal of Surgery* through an appreciation in 1949 and a special number on his 80th birthday. At this time his attitude to these tributes was expressed by his remark that "the kindness of myriads of friends has helped to make my entry into the eighties less sad and depressing than I had anticipated".

As a surgeon he was an acknowledged master.

"No man could have been as good as Gordon was on his day," writes T. H. S. "His gentle handling and ability to know where he was and what he was doing, in days when anæsthetics and other aids to surgery were only partly developed, was little short of miraculous. He was most at home in the abdomen and neck, less happy with bone work, and frankly declined to touch cerebral surgery. He pioneered thoracotomy in his early endeavours to treat cancer of the œsophagus, and in the full generosity of the man he provided every opportunity for his assistants to develop a specialty, even though he saw in this fragmentation the end of the era of the true general surgeon. He taught by example and by encouragement, he rarely criticised, but was unforgiving of carelessness or slackness. He never forgot a pupil and would do everything that he could do to help them in their careers. And it was not only his personal pupils he helped; anyone

could, and many did, seek his advice, which he gave in full measure. Generosity such as his has rarely been found."

M. W. once described work with Gordon-Taylor as "a wonderful education for a young and inexperienced house-surgeon, for he expected one to take a share in all that was going on and one's work was not limited to holding retractors and swabbing-up blood. He too regarded patients as human beings and he never gave up while there was the remotest chance of a successful issue to a case."

As a speaker and lecturer he was in a class by himself. He always said that his addresses took long preparation, but they gave an impression of spontaneity. His rounded prose stopped just short of the florid, and his delivery had a rhythm and force that made the speech as well as its substance a joy to listen to—and the more memorable because such oratory can now be heard so rarely. It was the same with his writing: he took immense care in preparation, polishing and repolishing. He wrote two monographs, the *Abdominal Injuries of Warfare* and *The Dramatic in Surgery*, and with Prof. Charles Wells a biography of Charles Bell which was only recently completed.

Outside surgery his acknowledged interests were few. He was a classical scholar and had been chairman of the Horatian Society. He was a devotee of good cricket, and when not otherwise occupied was to be seen in the afternoons at Lord's—outside which he met the accident which caused his death. His other relaxation, one might say, was walking, and to maintain physical fitness he walked several miles each day. He was also an excellent ballroom dancer and used to spend evenings after a long operating list in this way, and arrive at the Middlesex in the small hours to see how the patients operated on were progressing. His mode of life was selective, his habits abstemious. He was, for all practical purposes, a non-smoker, and he ate and drank little. He had never, he said, been in a public house or inside a cinema, and had only seen television when it related to surgery. His holidays were irregular and rare—a few days walking in his beloved Highlands or a day in bed reading the classics in an Edinburgh hotel. Occasionally he visited Continental clinics to study some particular interest, and on these occasions he often took as his guests his anæsthetist and assistants. After the war he was a much more travelled man, and international airlines knew him well. Distance meant little to him and he would willingly visit another continent for a few days if so requested. He would not refuse an invitation, however inconvenient, if it was to help British surgery.

His appearance and attire did not vary with the years, and the Harley Street area could recognise from afar the slim, alert, and dapper figure striding along coatless and with head just a little on one side. Always carefully dressed, he wore consistently a wing collar and bow tie; but his most characteristic foible was a carnation which was present winter and summer, at home or abroad. His voice was easy and charming: it never directly suggested the Scots ancestry of which he was so proud, but he was at all times fond of the Northern idiom.

"But the main characteristic of the man", as T. H. S. says, "was the friendship and loyalty that he evoked in everyone he met. When he made a friend he kept him, and each year hundreds of Christmas cards written in his own hand went out to people all over the world.

"It was not easy to know him intimately; there was a reserve beyond which only a few could penetrate to read his inmost thoughts. Surgery and all that it meant was open to everyone, as also were his hobbies of cricket and the classics; but apart from that there was only an occasional glimpse of the man—possibly afraid to reveal his generosity and sympathy for humanity in a modern age that he did not appreciate. Honours and applause meant less to him than the achievement of good surgery in relieving a fellow man's suffering. One of his great friends wrote of him as the most erudite of modern surgeons, as well as in his time the prince of craftsmen and (greatest of compliments) the 'doctor's surgeon'."

Another of his old house-surgeons, R. S. H., writes again of the devotion he inspired:

"He induced us to put forth a little more than our maximum effort, not by driving us, but by convincing us that the only activity in life which really mattered was surgery. He was kind to us in big and little ways. He supported us in our subsequent careers with a bias, a passion, and an energy which, in the end made the majority of us consultants. He was only once heard to make a slighting remark about a former house-surgeon—'he was not a good house-surgeon: he put on weight while he was with me'. He gave us a cystoscope and gold cuff-links at the end of our tenure of office. He paid us for helping him in private on so princely a scale that we, the unpaid house-surgeons of those days, could on the rare occasion of a free evening emulate our chief by going to the Savoy to dance. He told us stories of surgeons, of patients, of quaint events in his inimitable manner. He secretly provided comfort or convalescence for hospital patients, and we found out only by chance. He was a fabulous figure, and we copied his surgery and his gestures, his tricks of technique, and his mode of speech. We shall no longer receive little congratulatory notes on our small triumphs or hear some delightful anecdotes at a corner of Harley Street; but we shall remember G. G-T. to the end of our days and carry in our surgical substance things which he planted in us."

Gordon-Taylor was created K.B.E. in 1946. Lady Gordon-Taylor, whom he married in 1920, was Florence Mary Pegrume, F.R.S.A. She died in 1949, and they had no children.

ALAN FILMER ROOK

K.B.E., C.B., F.R.C.P., D.P.H.

Air Vice-Marshal Sir Alan Rook, whose death on Aug. 26 we announced last week, had made in both his medical careers—one in the Royal Air Force and the other at the University of Cambridge—a notable contribution to the health services of young people. He had great experience of the problems of young men and women under stress, and his sincerity and honesty inspired their confidence.

He was born at Forest Hill in 1892 and was educated at Mill Hill School and Guy's Hospital. A contemporary remembers him as a modest and gentle unassuming man who "was liked by everyone and was good at everything". After qualifying in 1915 he joined the R.A.M.C. and at the end of the war, after a brief period of postgraduate study at Guy's, he joined the R.A.F.

In 1922 he took part in a sandfly-fever investigation in the Middle East, and three years later he was posted to the Palestine General Hospital as medical officer with the rank of squadron-leader. Later he was transferred to Iraq and in due course became deputy principal medical officer. On his return to England in 1928 he spent some time in the R.A.F. pathological laboratory at Halton, and in 1936 he was appointed consultant in medicine at the Central Medical Establishment. Of Rook's work in the Service C. P. S. writes:

"During the earlier years there was not enough to exercise his eager and active mind, but when before the second war he became consulting physician at the Central Medical Establishment he found what he had long desired, scope for his clinical ability and interests, with able colleagues and excellent facilities for investigation. The war brought him further opportunity and full recognition of his talents. He enjoyed working with other consultants of his own calibre and teaching them to

apply their knowledge to Service problems, and they in turn appreciated his skill as a physician and his worth as a friend."

Rook was appointed C.B. in 1946 and K.B.E. in 1948. He was elected F.R.C.P. in 1939.

He retired from the R.A.F. in 1948 at the time when the University of Cambridge was starting a student health service, and Sir Lionel Whitby invited him to take charge of it: The new venture began in a hut at the back of Downing College, but some ten years later it moved to a new building at Fenners, with consulting-rooms, X-ray department, physiology room, and gymnasiums. In that time Rook devoted himself entirely to the health and welfare of Cambridge men and women, and he saw their problems gradually change, as physical disabilities—especially pulmonary tuberculosis—declined, while psychological problems became more important. After his retirement, two years ago, he stayed in the department to analyse the 15,000 case-records which had passed through his hands; but his long illness unfortunately interrupted his proposed correlation of academic performance, physical prowess, and mental stability.

A. L. B. writes:

"Shy and sensitive, with warm emotional reactions, Rook never succeeded fully in adapting himself to the critical Cambridge atmosphere. More than once it fell to me to fire the bullets that he manufactured because he could not trust himself to reply calmly on a matter about which he felt strongly. Perhaps his greatest contribution in Cambridge was the encouragement of the spirit of adventure in the young. With the approach of each long vacation the upper floor of our building at Fenners became strewn with first-aid kits for undergraduate expeditions, and he supplemented these with personal advice to each team. Characteristically he decided that one expedition was going to so remote a place that it must be supplied with morphine, and it became necessary to prolong the subsequent official correspondence until such time as the expedition returned, fortunately with the morphine untouched.

"Another activity to which he gave much time was the building up of an organisation whereby tuberculous students could continue their studies while under treatment. The rehabilitation of athletes after injury was another of his interests. As time went on his advice came to be sought on an extraordinary range of problems at all levels within the university. He was the sort of man that it is impossible to replace, for his niche is carved in the affections. Everyone respected Rook. They also liked him."

He is survived by his second wife, formerly Elizabeth Wilson, whom he married in 1946.

JAMES RUSSELL

C.B.E., M.B. Glasg., F.R.C.S.E., F.R.F.P.S.

Mr. Russell, consulting surgeon to the Victoria Infirmary, Glasgow, died at his home at Newton Mearns on Aug. 26 at the age of 78. He was a pioneer of orthopædic surgery in the West of Scotland, and it was largely through his efforts that the Philipshill Hospital at Busby was set up as an orthopædic annexe of the Victoria Infirmary.

After qualifying from the University of Glasgow in 1902 he held a number of house-appointments at the Victoria Infirmary, where eventually he was appointed visiting surgeon. His work to establish orthopædics as a specialty began during the 1914–18 war, and during the late war he was surgical director of the Western Scotland civil defence area. He helped to organise the emergency hospitals at Killearn, Ballochmyle, and Law. At Ballochmyle he started a jaw injury and plastic surgery unit. He was appointed C.B.E. in 1945. Three years later he retired from his hospital appointments, but he served as a member of the management committee of the Victoria hospital group.

A colleague, who first met Mr. Russell in 1937 or 1938 when he was recruiting staff for the new fracture clinic and orthopædic department which a year or two later he "imposed" on the Victoria Infirmary, writes:

"His enthusiasm for his new creation was boundless and his ability to get his way amazing. He seemed to prefer the indirect to the direct approach, but he knew where he was going and usually got there. He was a most staunch supporter of his staff and stuck up for their rights strenuously, and I personally found that despite a serious and, at the time, apparently bitter disagreement his friendship was not withdrawn. In fact later it increased and perhaps our difference was partly the reason, for if there was one quality he valued, and showed, it was a sturdy independence. He could not stand conceit and was constant in his criticism of bureaucracy and bureaucrats, with whom he always enjoyed a battle—sometimes carrying in his pocket letters to them which he would bring out and read aloud. They were never posted; but I suspect that they relieved his feelings, and probably the ammunition they contained got to the targets in the end. He was never in a hurry and even while still busy with work had time for long talks over cups of tea, playing havoc with the arrangements and plans of his impatient juniors. But for the patient listener it was never time wasted, for there was always a lesson in what he said—and at any rate it taught us the value of time. His talk was allusive and not always easy to follow; but it was full of homely phrases and often clear enough, as when he told us that someone was 'no thinkin' right' or 'no very stable, that yin'. He was not understood or appreciated by everyone, but his friends believe that he did a tremendous work and by them he will be sadly missed."

Mr. Russell is survived by a son and a daughter.

Dr. JONES-DAVIES

A colleague writes:

Dr. Jones-Davies' chief personal qualities were loyalty against any odds to all those with whom he came in contact, and humanity. "Each man is of importance to himself" was one of his favourite quotations, and he always bore this in mind in his work. He had great tact, and when I was seriously ill under his care he visited me daily without giving me the slightest inkling of the situation. His overall grasp of a medical case has helped us all to the wisest course many times. He had a lovable nature and a warm heart, and not seldom showed a really poetic turn of phrase.

Appointments

ANTON, H. C., M.B. Aberd., D.M.R.D.: radiologist (S.H.M.O.), Aberdeen General Hospital and Aberdeen special hospitals.
BUCHANAN, JESSIE R. G., M.B. Edin.: part-time S.H.M.O., department of venereology, General Infirmary, Leeds.
CAPON, MARGARET, M.B. Lond.: assistant M.O. and school M.O., Northamptonshire.
DAVIES, D. M., M.R.C.P.: S.H.M.O. in charge of the receiving room, London Hospital.
GRUENEBERG, R. H. K., M.D. Basle, F.R.C.S.: senior casualty officer, Kirkcaldy General Hospital.
LAVERICK, R. C., M.B. Leeds, D.P.H.: deputy M.O.H., Halifax.
LOCKEY, EUNICE, M.D., B.SC. Lond.: consultant pathologist, Royal Masonic Hospital, London.
MANNING, L. K., M.B. Lond., M.R.C.P.E.: assistant chest physician, Chesterfield and North Derbyshire area.
MCCOMB, T. N., M.B. Glasg.: assistant anæsthetist, Ballochmyle Hospital, Mauchline, Ayrshire.
OKOLSKI, STEFAN, M.B. Polish Sch. Med. Edin.: senior casualty officer, Wansbeck group of hospitals.
THOMPSON, B. A., M.B. Edin., F.R.C.S.E.: consultant surgeon, Scottish Borders Hospitals board of management.

The Hospital for Sick Children, Great Ormond Street, London:

ATWELL, J. D., M.B. Leeds, F.R.C.S.: surgical registrar.
DUDGEON, J. A., M.C., M.D. Cantab.: consultant pathologist in charge, department of microbiology.
GLOVER, W. J., M.B. Belf., F.F.A. R.C.S., D.OBST.: consultant anæsthetist.

Nottingham Health Services:

BOSTOCK, A. D., M.B. Manc., D.P.H.: senior M.O.
FRASER, I. G. P., M.B. Edin., D.P.H.: senior M.O.
MATHESON, K. W., M.B. Edin., D.C.H., D.P.H.: deputy M.O.H.
PALMER, W. L., M.B. Durh., D.T.M. & H., D.P.H.: senior assistant M.O.
PLOWRIGHT, NELLIE M., M.B. Birm., D.C.H., D.P.H.: senior assistant M.O.
STORY, DORIS, M.B. Durh., D.P.H.: senior assistant M.O.

Notes and News

THE CONGO

THE primary objective of the emergency period on the health side of the United Nations operation in the Congo [1 2] has been achieved, according to Dr. J. S. McKenzie Pollock, W.H.O. senior representative. There are now in the country enough medical personnel, consisting of Red Cross and Government teams, to staff all provincial and the main district hospitals, even if the hundred or so remaining Belgian doctors were to leave. There are 25 medical teams from 23 countries, coordinated by W.H.O.

W.H.O. gives news of the following teams besides those named last week [2]: two Canadian Red Cross; a second Australian Red Cross; a Pakistani Red Cross; an Iranian team; and a Swiss medical unit.

In addition there are 28 W.H.O. personnel, including the 15-member W.H.O. advisory team to the Central Ministry of Health. This team has completed a preliminary survey of the general health services of the country, and has made recommendations for a suggested permanent establishment in the Congo. To staff a basic health service, as recommended by the advisory team, about 650 medical personnel would be required in the following categories: doctors, pharmacists, dentists, nurses, midwives, sanitarians, biologists, sanitary engineers, and technicians. This number does not include provision for the training programme which will be needed over a long period gradually to qualify Congolese to fill the posts which, for the time being, will have to be staffed from outside. A detailed programme for such training of Congolese staff is being prepared by the W.H.O. advisory team, in consultation with the Ministry of Health. The province of Katanga is not included because its final personnel requirements are still unknown.

The second objective of the emergency period—to reactivate the public-health services of the country—has been only partly achieved, according to the W.H.O. report. Water-supplies in the large towns are being controlled and maintained with the help of W.H.O. and public-health engineers from Government teams. Short training courses have been organised for the Congolese maintenance staff of water-supply installations. Vector-control services and routine sanitation services have been restarted in most provincial centres. It has not yet been possible to reactivate the epidemic control services in rural districts, because of lack of supervisory personnel.

In Kasai province, a smallpox outbreak has been investigated and is considered to be a continuation of the local endemic situation. A smallpox outbreak in the Banningville area is being investigated. A plague outbreak reported from the Lac Albert area is being investigated by the health team at Bunia. Missionary and voluntary-agency medical services are proving their worth in the emergency; and, in many instances, missionary doctors are helping to maintain basic services at Government installations.

THE BEITS AND THEIR FELLOWSHIP

To perpetuate a name, the endowment of learning is at least as effective as memorial masonry. The Graham chair of pathology and the William Julius Mickle fellowship are as likely to survive as the Nelson column. But who were Graham and Mickle and why do we owe these endowments to their bounty? Because few can answer such questions without reference to the *D.N.B.*, the trustees of the Beit Memorial Fellowships have done well to celebrate the fiftieth anniversary of this foundation with a booklet which tells its history.[3]

In the first years of this century a plan was hatched to transfer the preclinical teaching of the medical sciences in London from the hospitals to two or three large institutes. For this purpose Alfred Beit, a former associate of Cecil Rhodes, subscribed £25,000 and promised a legacy of the same size. When, for better or worse, the scheme foundered on the opposition of the preclinical teachers, and the contributions were returned to the donors, Dr. James Kingston Fowler (in cooperation with Prof. E. H. Starling and Dr. John Rose Bradford) drafted a plan for using these funds to found three research fellowships in medicine. On Alfred Beit's death in 1906, his contribution and the rest of his large fortune went to his brother Otto (born in Hamburg in 1865) who had prospered in business in the City of London. Otto Beit took an active personal interest in Dr. Fowler's new proposals and eventually gave not only the £50,000 but enough to endow the fellowships, in his brother's memory, with £215,000.

It is because of these early connections that the Principal of London University was (and is) one of the trustees. The others were the founder until his death in 1930, Sir James Kingston Fowler, and three distinguished public figures. The trustees are advised by a small board made up of men of eminence in medicine and science, one of whom acts as secretary. The secretaries have been Dr. Fowler, Prof. T. R. Elliott, Sir Alan Drury, Prof. A. A. Miles, and now Sir Roy Cameron.

The first awards were made in 1909. In 1922 senior fellowships were added. From time to time the value of all fellowships has been increased. Until 1945 the fellows had to be of European descent, but the awards have since been open to any graduate of a university within the Commonwealth and the restriction to medical graduates has been removed. No money is ever given for bricks and mortar or for the expenses of research.

When the Beit fellowships were founded, the openings for the young man who wished to do research were few and restricted. The names of the early fellows and their subsequent careers (e.g., Thomas Lewis, T. R. Elliott, and Edward Mellanby) demonstrate that they filled a need. Since then two fellows have gained the Order of Merit; two have been Nobel prizemen; one has been ennobled and eight knighted; and forty-two have been elected to the Royal Society. Today the entry to a career in research is no harder than entry to surgery, but a Beit fellowship continues to be a mark of especial distinction. *Esto perpetua.*

AMENITY BEDS IN SCOTTISH HOSPITALS

THE Department of Health for Scotland is asking hospitals to review their provision of "amenity" beds and make it more widely known.

In the National Health Service patients who need privacy on medical grounds have the first claim to the single rooms or small wards. But, when not required for that purpose, beds in these rooms or wards may be given to patients willing to pay a charge. This charge varies from hospital to hospital, but it is always between a third and half of the cost of maintaining a patient in that hospital.

The Department hopes that hospitals will do what they can to provide amenity beds wherever the demand justifies it, but makes it clear to the public that willingness to pay for such a bed will not secure earlier admission to hospital: "as in the past, hospital admissions will be determined by medical priorities". The amenity bed is for National Health Service patients and not for the private patients of consultants.

PANORAMIC DENTAL RADIOGRAPHY

Now that more is known of the cumulative effect of radiation, greater attention is being given to the need for reducing exposure during radiographic examinations. Faster films and better-screened X-ray apparatus are available, and the application of television techniques has yielded the electronic image-intensifier.[1] Dental radiography makes only a small contribution to the total amount of man-made radiation to which a patient may be subjected, but it is one that could be reduced still further.

The usual dental X-ray machine operates at about 55–60 kV and the tube current is 10 milliamps (or 5 milliamps for some of the

1. See *Lancet*, Aug. 13, 1960, p. 358.
2. *ibid.* Sept. 3, 1960, p. 555.
3. The Beit Memorial Fellowships for Medical Research: 1909-1959. Privately printed by the trustees. 1960.

1. *Electronic Engg*, 1959, **31**, 352.

smaller sets); the exposure-time for a single film may be anything up to 1 second, although good periapical radiographs may be taken in 0·3–0·5 second on some of the faster films. As the American Academy of Oral Roentgenology points out, many dental surgeons over-expose and under-develop their films. A full-mouth examination usually requires seven films, and may need fourteen; and accordingly many workers consider that routine radiographic surveys —however valuable—of children's teeth are hardly justifiable, or even practicable.

Dr. S. Blackman, director of the department of radiology of the Royal Dental Hospital, has kindly given us details of a new Swiss X-ray tube—the 'Panoramix'—with which a view of the whole dentition may be taken on one film in 0·3 second.

This tube resembles the "insertion anode" type which has been in use in industry for some years. The focal spot is only 0·004 in. in diameter: and the anode, which is at the end of a tubular glass extension of the X-ray bulb, can be placed in the mouth. The anode emits a wide-angle divergent beam which gives an undistorted panoramic view of all the teeth and their supporting structures on a 10×4 in. film held against the outside of the face.

Measurements made on a prototype tube showed that, for an exposure of 0·15 milliamp-second at 56 kV the dose is about 2·5 roentgen at 1·5 cm. from the anode, falling to 1·5 roentgen at 5 cm., without additional filtration. The tongue, because of its nearness to the anode, would receive between 3 and 5 roentgens. Shields are being designed to reduce this dose, and also that to the brain, the spine, and lymphatic tissue. Dr. Blackman expects that the gonadal dose—already small in conventional dental radiography—will be too low to be measured by normal methods.

This tube is to form part of a mobile unit which is now under development, and a pilot survey to assess the possibilities of mass dental radiography for schoolchildren is planned for October.

University of London

The following degrees have been awarded:

M.D.—C. J. Wardle, M. L. N. Willoughby.
M.S.—Owen Daniel, A. J. Harrold.

Royal College of Physicians of London

Sir Francis Fraser will deliver the Harveian oration on Tuesday, Oct. 18, at 3 P.M., at the college, Pall Mall East, S.W.1. His subject will be the Challenge to the Medical Profession.

Association for the Study of Medical Education

This Association will hold a symposium at the Royal College of Physicians of London, Pall Mall East, S.W.1, on Friday, Dec. 2, on the functions and structure of the teaching hospital.

Scholarships to Winchester College

Wilson-Barkworth Fund—Grants from this fund are available to help in the education at Winchester College of sons of members of the Royal College of Surgeons of England. Further particulars may be had from the clerk to the trustees of the Fund, Messrs. Gray Bodsworth & Cobb, Duncombe Place, York.

Medical Research Council Fellowships

Applications are invited for the following travelling fellowships and scholarships available through the Council for 1961–62:

(1) Rockefeller travelling fellowships, (2) Sir Henry Wellcome travelling fellowships, (3) United States Public Health Service fellowships, (4) Lilly foreign fellowships, (5) Lederle travelling fellowships, (6) Dorothy Temple Cross research fellowships in tuberculosis, (7) Alexander Pigott Wernher travelling fellowships in ophthalmology and otology, (8) French exchange scholarships in medical science. Further information and application forms may be had from the secretary of the Council, 38, Old Queen Street, Westminster, S.W.1, and the closing date for applications is Oct. 31.

International Cancer Congress

This congress will be held in Moscow from July 23 to 28, 1962. Particulars may be had from the general secretary of the congress, Prof. L. Shabad, Academy of Medical Sciences of the U.S.S.R., 14, Solyanka, Moscow, U.S.S.R.

World Health Organisation

Dr. Fred Grundy, Mansel Talbot professor of preventive medicine in the Welsh National School of Medicine, Cardiff, has been appointed an assistant director-general of W.H.O. The position of fourth assistant director-general has lately been created, and as its first holder Dr. Grundy will be responsible for the divisions of public-health services, of health protection and promotion, and of education and training. He is expected to take up his duties at the beginning of 1961.

Dr. Grundy was born in 1905 in Bradford, Yorkshire, and graduated M.B. in the University of Leeds in 1927. After five years' hospital work he entered the public-health service and held appointments in Suffolk and Willesden, eventually becoming medical officer of health of Luton. He was called to the bar in 1931. Among his publications are two textbooks of preventive and social medicine, and he was a co-author of a study on undergraduate and postgraduate education in nineteen countries, which appeared in the W.H.O. monograph series. He also has acted as a W.H.O. consultant to the Expert Committee on Postgraduate Training in the Public Health Aspects of Nuclear Energy, and he has visited Ceylon to advise the Government on public-health law.

Occupational Health

A course on this subject will be held for general practitioners and industrial medical officers from Monday, Sept. 26, to Saturday, Oct. 1, at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1. Further particulars may be found in our advertisement columns.

International Congress of Neuropathology

This congress will be held in Munich from Sept. 4 to 8, 1961. Further particulars may be had from the general secretary of the congress, Prof. H. Jacob, Universitätsnervenklinik, Ortenbergstrasse 8, Marburg/Lahn, Germany. Intending contributors from Great Britain should forward titles without delay to Prof. C. E. Lumsden, School of Medicine, Leeds, 1.

Sir Gordon Covell has been awarded the Walter Reed medal of the American Academy of Science in recognition of his contributions to tropical medicine.

Lord Twining will give the inaugural address at King's College Hospital Medical School, Denmark Hill, London, S.E.5, on Friday, Sept. 30, at 3 P.M.

Particulars of a refresher course in ophthalmology to be held at the Courage Laboratory of the Royal Eye Hospital, St. George's Circus, London, S.E.1, may be had from Prof. Arnold Sorsby at the Courage Laboratory.

On Friday, Sept. 16, at 5.30 P.M., at the Whitely Wood Clinic, University of Sheffield, Dr. Karl Menninger, of Topeka, will speak on psychiatric case study.

Prof. R. E. Lane has been appointed a member of the Government's research study group on toxic chemicals used in agriculture and food storage, in succession to Dr. Donald Hunter who has resigned.

The annual dinner of the Yorkshire Glasgow Graduates Association will be held on Oct. 7 in the Hotel Metropole, Leeds, when Sir Compton Mackenzie will be the guest of honour. Further particulars may be had from Mr. James Wishart, 33, Manor Row, Bradford, 1.

The annual dinner of past and present men students of the Leeds School of Medicine will be held at the Griffin Hotel, Leeds, on Friday, Oct. 14, at 7 P.M. Further particulars and tickets (27*s.* 6*d.*) may be had from Mr. Jeffrey Ellis, at the medical school.

Dr. Hugh Garland, Dr. Michael Ashby, Dr. E. R. Bickerstaff, Dr. Roger Gilliatt, Dr. W. B. Matthews, Dr. Henry Miller, and Dr. B. G. Parsons-Smith are to visit Bucharest and other centres as guests of the Academy of Medical Sciences of the Rumanian People's Republic from Sept. 10 to 20.

CORRIGENDUM: *Detection of Epidemic Strains of* Staph. aureus.—In table III of the article by Dr. B. Moore (Aug. 27, p. 453) one strain of phage-type 29/52/52A/79/80 was shown as mercury-sensitive: in fact the single strain of this type examined was mercury-resistant. On the last line of the same table the phage-type should read: 29/52/52A/79. In fig. 3 the phage-type shown as 55/77 should be 75/77.